CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label No. EG913105772US
Date of Deposit October 21, 1996
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

MARK BOSSE
(Typed or Printed Name of Person Mailing Paper or Fee)

[signature]
(Signature of Person Mailing Paper or Fee)

Piperidine Compounds

Cross Referenced to Related Applications

This application is a continuation-in-part application of United States Patent Application Serial Number 08/702,308, filed August 23, 1996, which was a continuation-in-part application of United States Patent Application Serial Number 08/653,034, filed March 24, 1996, which was a continuation-in-part application of United States Patent Application Serial Number 08/606,624, filed February 26, 1996, which was a continuation-in-part application of United States Patent Application Serial Number 08/580,567, filed December 29, 1995, which was a continuation-in-part application of United States Patent Application Serial Number 08/476,946, filed June 6, 1995, which was a continuation-in-part application of United States Patent Application Serial Number 08/395,245, filed February 27, 1995, all of which are incorporated herein by reference in their entirety. This application is related to United States Patent Application Serial Number 08/701,942, filed August 23, 1996, which describes methods of making carbocyclic compounds and is incorporated by reference in its entirety.

Background of the Invention

Field of the Invention

Neuraminidase (also known as sialidase, acylneuraminyl hydrolase, and EC 3.2.1.18) is an enzyme common among animals and a number of

microorganisms. It is a glycohydrolase that cleaves terminal alpha-ketosidically linked sialic acids from glycoproteins, glycolipids and oligiosaccharides. Many of the microorganisms containing neuraminidase are pathogenic to man and other animals including fowl, horses, swine and seals. Organisms having N-acetylneuraminidases include bacteria such as *Vibrio cholerae*, *C. perfringens* and *Streptococcus* sp. and viruses such as influenza virus, and parainfluenza virus.

Influenza neuraminidase has been implicated in the pathogenicity of influenza viruses. It is thought to help the elution of newly synthesized virons from infected cells and assist in the movement of the virus (through its hydrolase activity) through the mucus of the respiratory tract.

Brief Description of Related Art

Itzstein, M. von et al.; "Nature", 363(6428):418-423 (1993), discloses the rational design of sialidase-based inhibitors of influenza virus replication.

Colman, P. M. et al.; International Patent Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date April 30, 1992), Itzstein, L. M. von et al.; European Patent Publication No. 0 539 204 A1 (EP App. No. 92309684.6, publication date April 28, 1993), and Itzstein, L. M. von et al.; International Publication No. WO 91/16320 (Int. App. No. PCT/AU91/00161, publication date October 31, 1991) disclose compounds that bind neuraminidase and are asserted to exhibited antiviral activity *in vivo*.

Umezawa, H; et al.; J. Antibiotics, **1974**, 27, 963-969, discloses the isolation of Siastatin B. Nishimura, Y.; et al.; J. Am. Chem. Soc., **1988**, 110, 7249-7250; and Bull. Chem. Soc. Jpn., **1992**, 65, 978-986, disclose the total synthesis of Siastatin B. Nishimura, Y.; et al.; J. Antibiotics, **1992**, 45(10), 1662-1668; **1993**, 46(2), 300-309; 46(12), 1883-1889; **1994**, 47(1), 101-107; and Nat. Prod. Lett., **1992**, 1(1), 39-44; as well as Japanese Patent Applications 92-287381 (October 26, 1992); 90-201437 (July 31, 1990); 88-125020 (May 24, 1988) and 50046895 (April 25, 1975) disclose synthetic transformations of Siastatin B including certain dehydrosiastatin B analogs. Zbiral, E.; et al.; Liebigs Ann. Chem., **1991**, 129-134; and von Itzstein, M.; et al.; Carbohydrate Res., **1993**, 244, 181-185, disclose synthetic transformation of the hydroxy group at C4 of sialic acid to an amino group.

Objects of the Invention

Selected embodiments of the invention satisfy one or more of the following objects:

A principal object of the invention is inhibition of bactria and viruses, in particular influenza viruses. In particular, an object is inhibition of glycolytic enzymes such as neuraminidase, in particular the selective inhibition of viral or bacterial neuraminidases.

An additional object of the invention is to provide neuraminidase inhibitors that have a retarded rate of urinary excretion, that enter into nasal or pulmonary secretions from the systemic circulation, that have sufficient oral bioavailability to be therapeutically effective, that possess elevated potency, that exhibit clinically acceptable toxicity profiles and have other desirable pharmacologic properties.

Another object is to provide improved and less costly methods for synthesis of neuraminidase inhibitors.

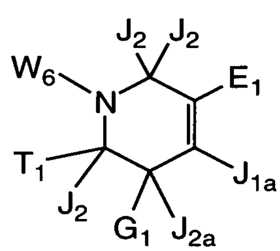
A still further object is to provide improved methods for administration of known and novel neuraminidase inhibitors.

An additional object is to provide compositions useful in preparing polymers, surfactants or immunogens and for use in other industrial processes and articles

These and other objects will be readily apparent to the ordinary artisan from consideration of the invention as a whole.

Summary of the Invention

Compounds, or compositions having formula (IX) are provided herein:



(IX)

wherein

E_1 is $-(CR_1R_1)_{m1}W_1$;

G_1 is N_3, -CN, -OH, $-OR_{6a}$, $-NO_2$, or $-(CR_1R_1)_{m1}W_2$;

T_1 is $-NR_1W_3$, or a heterocycle;

J_{1a} are independently R_1, Br, Cl, F, I, CN, NO_2 or N_3;

J_2 and J_{2a} are independently H or R_1;

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, $=N(R_1)$ or $=N(R_{6b})$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5;

W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(NR_{6b})(N(H)(R_{6b}))$, $-C(N(H)(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$; and

each m_1 is independently an integer from 0 to 2;

provided, however, that compounds are excluded wherein J_{1a} is H, each J_2 is H, J_{2a} is H and T_1 is $-N(H)(Ac)$ and:

E_1 is $-CO_2H$ or $-CO_2CH_3$,
G_1 is -OBoc, and
W_6 is Boc;

E_1 is $-CO_2H$ or $-CO_2CH_3$,
G_1 is -OH, and
W_6 is H;

E_1 is $-CO_2H$, $-CO_2CH_3$ or $-CO_2Bn$
G_1 is -OH, and
W_6 is Boc;

E_1 is $-CONH_2$,
G_1 is -OH, and
W_6 is Boc or H;

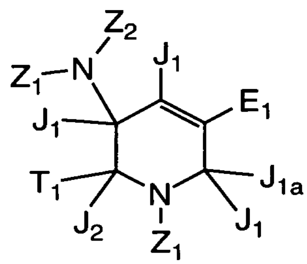
E_1 is $-CO_2H$ or $-CO_2CH_3$,
G_1 is OH, and
W_6 is Bn; or

E_1 is $-CO_2H$ or $-CO_2CH_3$,
G_1 is -OH, and
W_6 is $-CH_2CH(OH)CH_2(OH)$;

wherein Bn is benzyl and Boc is $-CO_2C(CH_3)_3$;
and the salts, solvates, resolved enantiomers and purified diastereomers

thereof.

In another embodiment, compounds, or compositions having formula (X) are provided herein:



(X)

wherein

one Z_1 is W_6 and the other Z_1 is G_1;

Z_2 is H or W_6;

E_1 is $-(CR_1R_1)_{m1}W_1$;

G_1 is -OH, $-OR_{6a}$, or $-(CR_1R_1)_{m1}W_2$;

T_1 is $-NR_1W_3$ or a heterocycle;

J_1 and J_{1a} are independently R_1, Br, Cl, F, I, CN, NO_2 or N_3;

J_2 is H or R_1;

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, $=N(R_1)$ or $=N(R_{6b})$;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12

carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_1 is a group comprising an acidic hydrogen, a protected acidic group, or an R_{6c} amide of the group comprising an acidic hydrogen;

W_2 is H or a group comprising a basic heteroatom or a protected basic heteroatom, or an R_{6b} amide of the basic heteroatom;

W_3 is W_4 or W_5;

W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(NR_{6b})(N(H)(R_{6b}))$, $-C(N(H)(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$;

each m_1 is independently an integer from 0 to 2;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof.

In another embodiment of the invention a compound or composition of the invention is provided that further comprises a pharmaceutically-acceptable carrier.

In another embodiment of the invention the activity of neuraminidase is inhibited by a method comprising the step of treating a sample suspected of containing neuraminidase with a compound or composition of the invention.

Another embodiment of the invention provides a method for inhibiting the activity of neuraminidase comprising the step of contacting a sample suspected of containing neuraminidase with the composition

embodiments of the invention.

Detailed Description

Compositions of the Invention.

The compounds of this invention exclude compounds heretofore known. However, as will be further apparent below, in other embodiments, it is within the invention to use for antiviral purposes known compounds heretofore only produced and used as intermediates in the preparation of antiviral compounds. With respect to the United States, the compounds or compositions herein exclude compounds that are anticipated under 35 USC §102 or obvious under 35 USC §103. In particular, the claims herein shall be construed as excluding the compounds which are anticipated by or not possessing novelty over Nishimura, Y.; et al.; J. Am. Chem. Soc., **1988**, 110, 7249-7250; and Bull. Chem. Soc. Jpn., **1992**, 65, 978-986, disclose the total synthesis of Siastatin B. Nishimura, Y.; et al.; J. Antibiotics, **1992**, 45(10), 1662-1668; **1993**, 46(2), 300-309; 46(12), 1883-1889; **1994**, 47(1), 101-107; Nat. Prod. Lett., **1992**, 1(1), 39-44; and Japanese Patent Applications 92-287381 (October 26, 1992); 90-201437 (July 31, 1990); 88-125020 (May 24, 1988) and 50046895 (April 25, 1975).

In a further embodiment, the compounds of this invention are those in which W_6 is not $-CH_2OH$, $-CH_2OAc$, or $-CH_2OCH_2Ph$.

In a further embodiment, the compounds of this invention are those in which E_1 is not $-CH_2OH$, $-CH_2OTMS$, or -CHO.

In a further embodiment, the compounds of this invention are those in which W_6 is not polyhydroxyalkane, especially $-CH(OH)CH(OH)CH_2OH$. In a further embodiment, W_6 is a branched chain group R_5 as described below or a carbocycle which is substituted with at least one group R_5.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R_1" or "R_{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem.

Soc.", 82:5566 (1960).

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

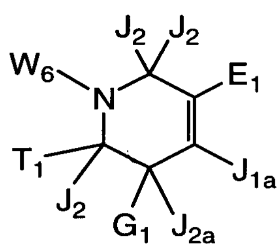
By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine,

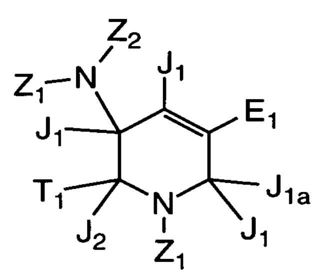
piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Alkyl" as used herein, unless stated to the contrary, is C_1-C_{12} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$). Examples of alkyl groups appear in Table 2 as groups 2-5, 7, 9, and 100-399.

The compositions of the invention comprise compounds of either formula:



(IX) or



(X)

In the typical embodiment, the compounds of Formula IX are chosen.

J_1 and J_{1a} are independently R_1, Br, Cl, F, I, CN, NO_2 or N_3, typically R_1 or F, more typically H or F, more typically yet H.

J_2 and J_{2a} are independently H or R_1, typically H.

One Z_1 of Formula X is W_6 and the other is G_1;

Z_2 of Formula X is H or W_6, typically H;

E_1 is $-(CR_1R_1)_{m1}W_1$.

Typically, R_1 is H or alkyl of 1 to 12 carbon atoms, usually H or an alkyl of 1 to 4 or 5 to 10 carbon atoms, still more typically, H or an alkyl of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms, more typically yet, H or an alkyl of 1 to 3 carbon atoms selected from methyl, ethyl, n-propyl, and i-propyl. Most typically R_1 is H.

m1 is an integer of 0 to 2, typically 0 or 1, most typically 0.

m2 is an integer of 0 to 1.

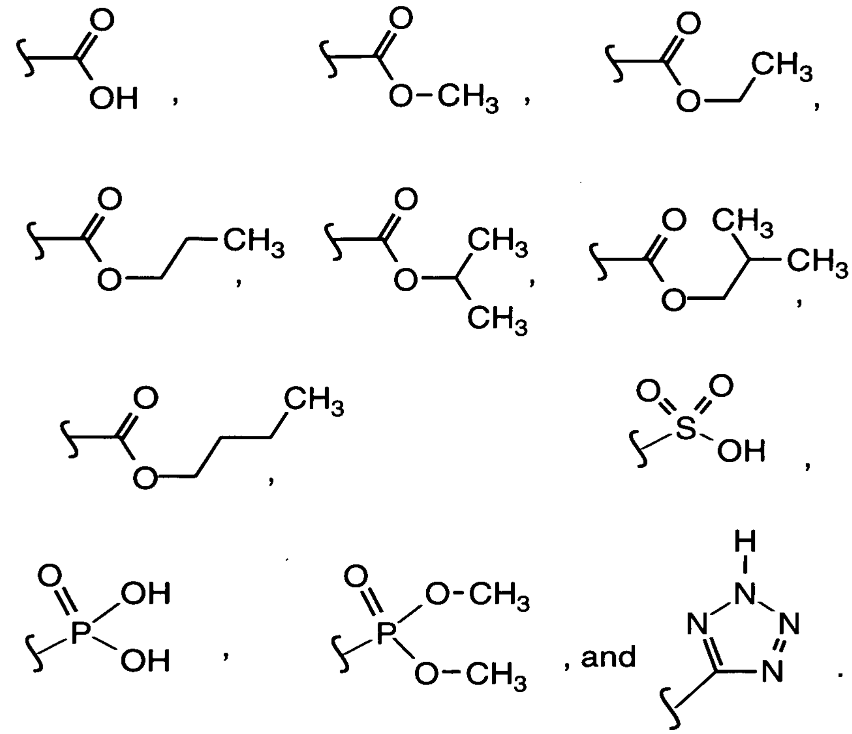
m3 is an integer of 1 to 3.

W_1 is a group comprising an acidic hydrogen, a protected acidic group or an R_{6c} amide of the group comprising an acidic hydrogen which, within the context of the invention, means a group having a hydrogen atom that can be removed by a base yielding an anion or its corresponding salt or solvate. The general principles of acidity and basicity of organic materials are well understood and are to be understood as defining W_1. They will not be detailed here. However, a description appears in Streitwieser, A.; and Heathcock, C. H.; "Introduction to Organic Chemistry, Second Edition" (Macmillan, New York, 1981), pages 60-64. Generally, acidic groups of the invention have pK values less than that of water, usually less than pK = 10, typically less than pK = 8, and frequently less than pK = 6. They include tetrazoles and the acids of carbon, sulfur, phosphorous and nitrogen, typically the carboxylic, sulfuric, sulfonic, sulfinic, phosphoric and phosphonic acids, together with the R_{6c} amides and R_{6b} esters of those acids (R_{6c} and R_{6b} are defined below). Exemplary W_1 are $-CO_2H$, $-CO_2R_{6a}$. $-OSO_3H$, $-SO_3H$, $-SO_2H$, $-OPO_3H_2$, $-PO_3(R_{6a})_2$, $-PO_3H_2$, $-PO_3(H)(R_{6a})$, and $-OPO_3(R_{6a})_2$. E_1 typically is W_1, and W_1 typically is $-CO_2H$, $-CO_2R_{6a}$, $-CO_2R_4$ or CO_2R_1, and most typically is CO_2R_{14} wherein R_{14} is normal or terminally secondary C_1-C_6 alkyl.

W_1 may also be a protected acidic group, which, within the context of the invention means an acidic group as described above that has been protected by one of the groups commonly used in the art for such groups and are described below under R_{6a}. More typically, protected W_1 is $-CO_2R_1$, $-SO_3R_1$, $-S(O)OR_1$, $-P(O)(OR_1)_2$, $-C(O)NHSO_2R_4$, or $-SO_2NHC(O)-R_4$, wherein R_1 and R_4 are defined above.

Most typically, E_1 is selected from $-C(O)O(CH_2)_bCH((CH_2)_cCH_3)_2$ where

b = 0 to 4, c = 0 to 4, and b + c = 1 to 4, or from the group of



Exemplary E_1 groups are listed in Tables 3a through 3b.

G_1 of Formula X is -OH, OR_{6a}, or $-(CR_1R_1)_{m1}W_2$, G_1 of Formula IX is N_3, -CN, -OH, OR_{6a}, $-NO_2$ or $-(CR_1R_1)_{m1}W_2$, wherein R_1 and m1 are defined above. Ordinarily, G_1 of Formula (IX) is $-(CR_1R_1)_{m1}W_2$ and G_1 of Formula (X) is H.

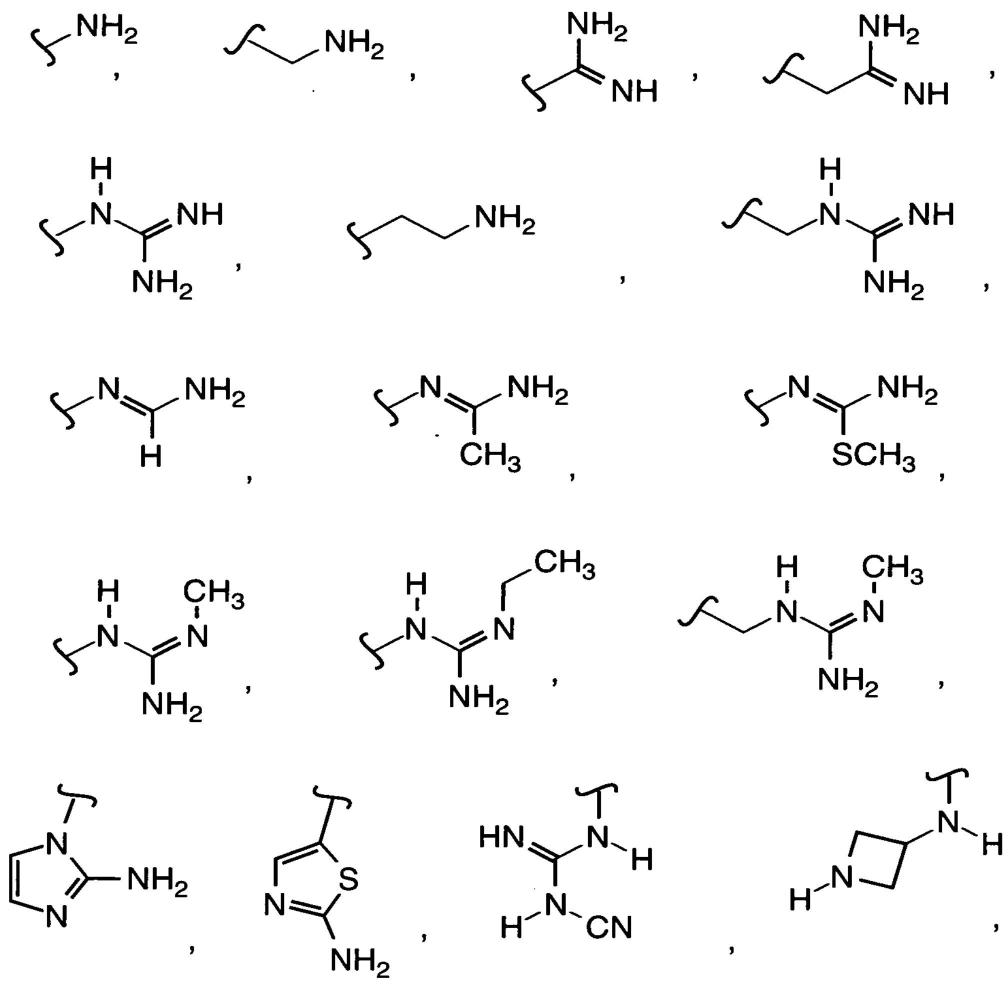
W_2 of Formula (X) is H or a group comprising a basic heteroatom, a protected basic heteroatom or an R_{6b} amide of the basic heteroatom. W_2 of Formula (IX) is a group comprising a basic heteroatom, a protected basic heteroatom or an R_{6b} amide of the basic heteroatom. W_2 generally comprises a basic heteroatom, which, within the context of the invention means an atom other than carbon which is capable of protonation, typically by an acidic hydrogen having an acidity in the range described above for W_1. The basic principles of basicity are described in Streitwieser and Heathcock (*op. cit.*) and provide meaning for the term basic heteroatom as will be understood by those ordinarily skilled in the art. Generally, the basic heteroatoms employed in the compounds of the invention have pK values for the corresponding protonated form that are in the range of values described above for W_1. Basic heteroatoms include the heteroatoms common in organic compounds which

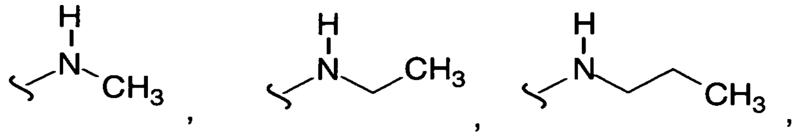
have an un-shared, non-bonding, n-type, or the like, electron pair. By way of example and not limitation, typical basic heteroatoms include the oxygen, nitrogen, and sulfur atoms of groups such as alcohols, amines, amidines, guanidines, sulfides, and the like, frequently, amines, amidines and guanidines. Ordinarily, W_2 is amino or an amino alkyl (generally lower alkyl C_1 to C_6) group such as aminomethyl, aminoethyl or aminopropyl; an amidinyl, or an amidinoalkyl group such as amidinomethyl, amidinoethyl, or amidinopropyl; or guanidinyl, or a guanidinoalkyl group such as guanidinomethyl, guanidinoethyl, or guanidinopropyl (in each instance wherein the alkyl group serves to bridge the basic substituent to the carbocyclic ring). More typically, W_2 is amino, amidino, guanidino, heterocycle, heterocycle substituted with 1 or 2 amino or guanidino groups (usually 1), or an alkyl of 2 to 3 carbon atoms substituted with amino or guanidino, or such alkyl substituted with an amino and a second group selected from the group consisting of hydroxy and amino. The heterocycles useful as W_2 include typically N or S-containing 5 or 6 membered rings, wherein the ring contains 1 or 2 heteroatoms. Such heterocycles generally are substituted at ring carbon atoms. They may be saturated or unsaturated and may be linked to the core cyclohexene by lower alkyl (m1=1 or 2) or by $-NR_1-$. Still more typically, W_2 is $-NHR_1$, $-C(NH)(NH_2)$, $-NR_1-C(NR_1)(NR_1R_3)$, $-NH-C(NH)(NHR_3)$, $-NH-C(NH)(NHR_1)$, $-NH-C(NH)NH_2$, $-CH(CH_2NHR_1)(CH_2OH)$, $-CH(CH_2NHR_1)(CH_2NHR_1)$, $-CH(NHR_1)-(CR_1R_1)_{m2}-CH(NHR_1)R_1$, $-CH(OH)-(CR_1R_1)_{m2}-CH(NHR_1)R_1$, or $-CH(NHR_1)-(CR_1R_1)_{m2}-CH(OH)R_1$, $-(CR_1R_1)_{m2}-S-C(NH)NH_2$, $-N{=}C(NHR_1)(R_3)$, $-N{=}C(SR_1)N(R_1)_2$, $-N(R_1)C(NH)N(R_1)C{=}N$, or $-N{=}C(NHR_1)(R_1)$; wherein each m2 is ordinarily 0, and ordinarily R_1 is H and R_3 is $C(O)N(R_1)_2$.

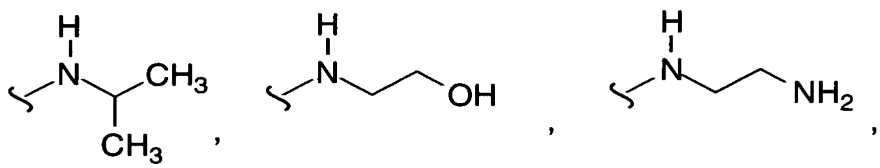
W_2 optionally is a protected basic heteroatom which within the context of the invention means a basic heteroatom as described above that has been protected by R_{6b} such as one of the groups common in the art. Such groups are described in detail in Greene (*op. cit.*) as set forth below. Such groups include by way of example and not limitation, amides, carbamates, amino acetals, imines, enamines, N-alkyl or N-aryl phosphinyls, N-alkyl or N-aryl sulfenyls or sulfonyls, N-alkyl or N-aryl silyls, thioethers, thioesters, disulfides, sulfenyls, and the like. In some embodiments, the protecting

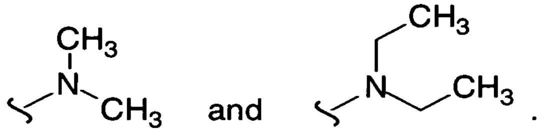
group R_{6b} will be cleavable under physiological conditions, typically it will be cleavable *in vivo* where, for example, the basic heteroatom forms an amide with an organic acid or an amino acid such as a naturally occurring amino acid or a polypeptide as described below for the R_{6a} group.

Typically G_1 of Formula (X) is H and G_1 of Formula (IX) is selected from the group consisting of:



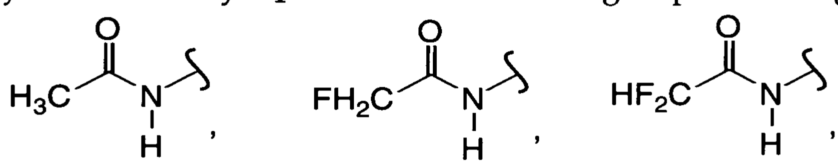


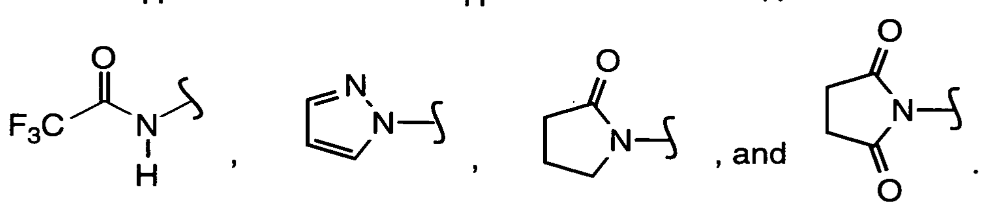




Further exemplary G_1 groups are listed in Table 4.

T_1 is $-NR_1W_3$, $-R_3$, $-R_5$ or heterocycle. Typically T_1 is $-NR_1W_3$ or heterocycle. Generally T_1 is selected from the group consisting of:





Exemplary T_1 groups are listed in Table 5.

W_3 is W_4 or W_5, wherein W_4 is R_5 or $-C(O)R_5$, $-C(O)W_5$, $-SO_2R_5$, or $-SO_2W_5$. Typically, W_3 is $-C(O)R_5$ or W_5.

R_2 is independently R_3 or R_4 as defined below, with the proviso that each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$,

$-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, $=N(R_1)$, $=N(R_{6b})$ or W_5. Typically R_3 is F, Cl, -CN, N_3, NO_2, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-NR_1C(O)R_1$, $-N(R_{6b})C(O)R_1$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, or =O. More typical R_3 groups comprising R_{6b} include $-C(O)N(R_{6b})_2$ or $-C(O)N(R_{6b})(R_1)$. More typically yet R_3 is F, Cl, -CN, N_3, $-OR_1$, $-N(R_1)_2$, $-SR_1$, $-C(O)OR_1$, $-OC(O)R_1$, or =O. More typically still, R_3 is F, $-OR_1$, $-N(R_1)_2$, or =O. In the context of the present application, "=O" denotes a double bonded oxygen atom (oxo), and "=S" $=N(R_{6b})$ and "$=N(R_1)$" denote the sulfur and nitrogen analogs.

R_4 is alkyl of 1 to 12 carbon atoms, and alkynyl or alkenyl of 2 to 12 carbon atoms. The alkyl R_4's are typically of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and the alkenyl and alkynyl R_4's are typically of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms. R_4 ordinarily is alkyl (as defined above). When R_4 is alkenyl it is typically ethenyl ($-CH=CH_2$), 1-prop-1-enyl ($-CH=CHCH_3$), 1-prop-2-enyl ($-CH_2CH=CH_2$), 2-prop-1-enyl ($-C(=CH_2)(CH_3)$), 1-but-1-enyl ($-CH=CHCH_2CH_3$), 1-but-2-enyl ($-CH_2CH=CHCH_3$), 1-but-3-enyl ($-CH_2CH_2CH=CH_2$), 2-methyl-1-prop-1-enyl ($-CH=C(CH_3)_2$), 2-methyl-1-prop-2-enyl ($-CH_2C(=CH_2)(CH_3)$), 2-but-1-enyl ($-C(=CH_2)CH_2CH_3$), 2-but-2-enyl ($-C(CH_3)=CHCH_3$), 2-but-3-enyl ($-CH(CH_3)CH=CH_2$), 1-pent-1-enyl ($-C=CHCH_2CH_2CH_3$), 1-pent-2-enyl ($-CHCH=CHCH_2CH_3$), 1-pent-3-enyl ($-CHCH_2CH=CHCH_3$), 1-pent-4-enyl ($-CHCH_2CH_2CH=CH_2$), 2-pent-1-enyl ($-C(=CH_2)CH_2CH_2CH_3$), 2-pent-2-enyl ($-C(CH_3)=CH_2CH_2CH_3$), 2-pent-3-enyl ($-CH(CH_3)CH=CHCH_3$), 2-pent-4-enyl ($-CH(CH_3)CH_2CH=CH_2$) or 3-methyl-1-but-2-enyl ($-CH_2CH=C(CH_3)_2$). More typically, R_4 alkenyl groups are of 2, 3 or 4 carbon atoms. When R_4 is alkynyl it is typically ethynyl ($-C\equiv CH$), 1-prop-1-ynyl ($-C\equiv CCH_3$), 1-prop-2-ynyl ($-CH_2C\equiv CH$), 1-but-1-ynyl ($-C\equiv CCH_2CH_3$), 1-but-2-ynyl ($-CH_2C\equiv CCH_3$), 1-but-3-ynyl ($-CH_2CH_2C\equiv CH$), 2-but-3-ynyl ($CH(CH_3)C\equiv CH$), 1-pent-1-ynyl ($-C\equiv CCH_2CH_2CH_3$), 1-pent-2-ynyl

($-CH_2C{\equiv}CCH_2CH_3$), 1-pent-3-ynyl ($-CH_2CH_2C{\equiv}CCH_3$) or 1-pent-4-ynyl ($-CH_2CH_2CH_2C{\equiv}CH$). More typically, R_4 alkynyl groups are of 2, 3 or 4 carbon atoms.

R_5 is R_4, as defined above, or R_4 substituted with 0 to 3 R_3 groups. Typically R_5 is an alkyl of 1 to 4 carbon atoms substituted with 0 to 3 fluorine atoms.

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups. As defined above for R4, R_{5a}'s are of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms when alkylene and of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms when alkenylene or alkynylene. Each of the typical R_4 groups is a typical R_{5a} group with the proviso that one of the hydrogen atoms of the described R_4 group is removed to form the open valence to a carbon atom through which the second bond to the R_{5a} is attached.

R_{14} is normal or terminally secondary C_1-C_6 alkyl.

W_5 is a carbocycle or heterocycle, with the proviso that each W_5 is independently substituted with 0 to 3 R_2 groups. W_5 carbocycles and T_1 and W_5 heterocycles are stable chemical structures. Such structures are isolatable in measurable yield, with measurable purity, from reaction mixtures at temperatures from -78°C to 200°C. Each W_5 is independently substituted with 0 to 3 R_2 groups. Typically, T_1 and W_5 are a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. More typically, T_1 or W_5 has 3 to 10 ring atoms, still more typically, 3 to 7 ring atoms, and ordinarily 3 to 6 ring atoms. The T_1 and W_5 rings are saturated when containing 3 ring atoms, saturated or monounsaturated when containing 4 ring atoms, saturated, or mono- or diunsaturated when containing 5 ring atoms, and saturated, mono- or diunsaturated, or aromatic when containing 6 ring atoms. Unsaturation of the W_5 rings include internal and external unsaturation wherein the external incorporates a ring atom.

When W_5 is carbocyclic, it is typically a 3 to 7 carbon monocycle or a 7 to 12 carbon atom bicycle. More typically, W_5 monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. W_5 bicyclic carbocycles typically have 7 to 12 ring atoms arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, still more typically, 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6]

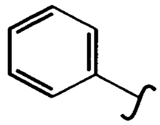
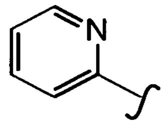
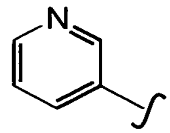
system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

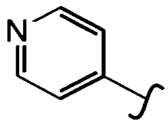
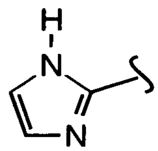
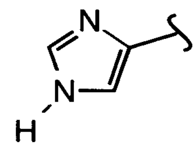
A T_1 or W_5 heterocycle is typically a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). More typically, T_1 and W_5 heterocyclic monocycles have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S), still more typically, 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). T_1 and W_5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system, still more typically, 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system.

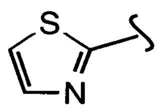
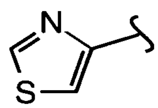
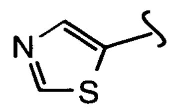
Typically T_1 and W_5 heterocycles are selected from pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, or pyrrolyl.

More typically, the heterocycle of T_1 and W_5 is bonded through a carbon atom or nitrogen atom thereof. Still more typically T_1 heterocycles are bonded by a stable covalent bond through a nitrogen atom thereof to the cyclohexene ring of the compositions of the invention and W_5 heterocycles are bonded by a stable covalent bond through a carbon or nitrogen atom thereof to the cyclohexene ring of the compositions of the invention. Stable covalent bonds are chemically stable structures as described above.

W_5 optionally is selected from the group consisting of:

 ,  ,  ,

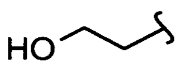
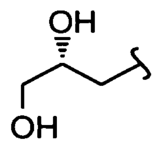
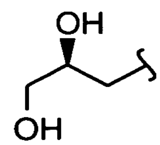
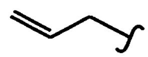
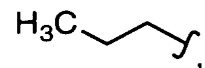
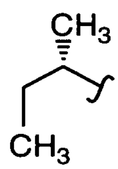
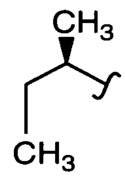
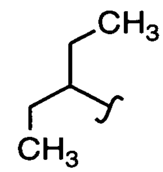
 ,  ,  ,

 ,  , and  .

W_6 is $-R_5$, $-W_5$, $-R_{5a}W_5$, $-C(O)OR_{6a}$, $-C(O)R_{6c}$, $-C(O)N(R_{6b})_2$, $-C(NR_{6b})(N(R_{6b})_2)$, $-C(NR_{6b})(N(H)(R_{6b}))$, $-C(N(H)(N(R_{6b})_2)$, $-C(S)N(R_{6b})_2$, or $-C(O)R_2$, typically W_6 is $-R_5$, $-W_5$, or $-R_{5a}W_5$; in some embodiments, W_6 is R_1, $-C(O)-R_1$, $-CHR_1W_7$, $-CH(R_1)_aW_7$, $-CH(W_7)_2$, (where, W_7 is monovalent a is 0 or 1, but is 0 when W_7 is divalent) or $-C(O)W_7$. In some embodiments, W_6 is $-CHR_1W_7$ or $-C(O)W_7$, or W_6 is $-(CH_2)_{m1}CH((CH_2)_{m3}R_3)_2$, $-(CH_2)_{m1}C((CH_2)_{m3}R_3)_3$; $-(CH_2)_{m1}CH((CH_2)_{m3}R_{5a}W_5)_2$; $-(CH_2)_{m1}CH((CH_2)_{m3}R_3)((CH_2)_{m3}R_{5a}W_5)$; $-(CH_2)_{m1}C((CH_2)_{m3}R_3)_2(CH_2)_{m3}R_{5a}W_5)$, $(CH_2)_{m1}C((CH_2)_{m3}R_{5a}W_5)_3$ or $-(CH_2)_{m1}C((CH_2)_{m3}R_3)((CH_2)_{m3}R_{5a}W_5)_2$; and wherein m_3 is an integer from 1 to 3.

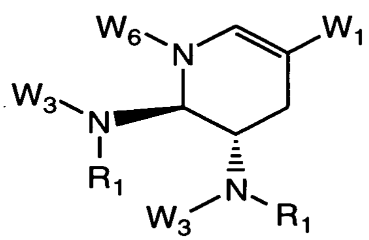
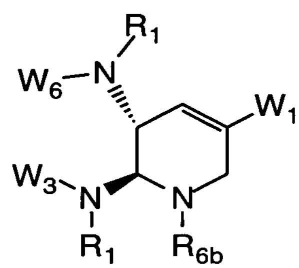
W_7 is R_3 or R_5, but typically is alkyl of 1 to 12 carbons substituted with 0 to 3 R_3 groups, the latter typically selected from the group consisting of $-NR_1(R_{6b})$, $-N(R_{6b})_2$, $-OR_{6a}$, or SR_{6a}. More typically, W_7 is $-OR_1$ or an alkyl of 3 to 12 carbon atoms substituted with OR_1.

In general, W_6 is R_1-, $-CHR_1W_7$,

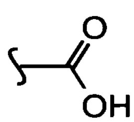
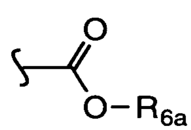
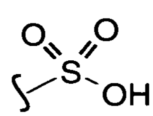
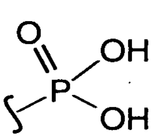
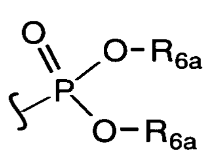
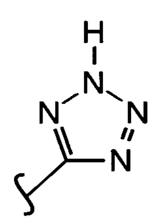
,
,
,
,
,
,
,
, and
.

Exemplary W6 groups are listed in Table 2.

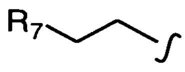
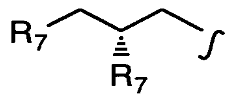
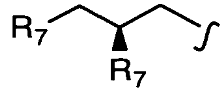
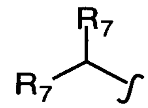
An embodiment of the invention comprises a compound of the formula:


(XI)
or

(XIII)
.

wherein each R1 and R6b are typically H, and W2 is typically selected from the group consisting of:

,
,
,
,
, and
;

and W6 is one of:

 ,  ,  , and  ;

wherein R7 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-OCH_3$, -OAc ($-O-C(O)CH_3$), -OH, $-NH_2$, or -SH, typically H, $-CH_3$ or $-CH_2CH_3$.

Groups R_{6a} and R_{6b} are not critical functionalities and may vary widely. When not H, their function is to serve as intermediates for the parental drug substance. This does not mean that they are biologically inactive. On the contrary, a principal function of these groups is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs are absorbed more effectively than the parental drug they in fact often possess greater potency in vivo than the parental drug. When not hydrogen, R_{6a} and R_{6b} are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting pro-functionality products, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

R_{6a} is H or an ether- or ester-forming group. "Ether-forming group" means a group which is capable of forming a stable, covalent bond between the parental molecule and a group having the formula:

$$\int\!\!-O-V_a(V_1)_3\ ,\quad \int\!\!-O-V_a(V_1)(V_2)\ ,\quad \int\!\!-O-V_a(V_3)$$

$$\int\!\!-O-V_b(V_1)_2\ ,\quad \int\!\!-O-V_b(V_2)\ ,\ \text{or}\quad \int\!\!-O-V_c(V_1)$$

Wherein V_a is a tetravalent atom typically selected from C and Si; V_b is a trivalent atom typically selected from B, Al, N, and P, more typically N and P; V_c is a divalent atom typically selected from O, S, and Se, more typically S; V_1 is a group bonded to V_a, V_b or V_c by a stable, single covalent bond, typically V_1 is W_6 groups, more typically V_1 is H, R_2, W_5, or $-R_{5a}W_5$, still more typically H or R_2; V_2 is a group bonded to V_a or V_b by a stable, double covalent bond, provided that V_2 is not =O, =S or =N-, typically V_2 is $=C(V_1)_2$ wherein V_1 is as described above; and V_3 is a group bonded to V_a by a stable, triple covalent bond, typically V_3 is $\equiv C(V_1)$ wherein V_1 is as described above.

"Ester-forming group" means a group which is capable of forming a

stable, covalent bond between the parental molecule and a group having the formula:

$$\wr\!-\!O\!-\!V_a(V_1)(V_4)\,,\qquad \wr\!-\!O\!-\!V_b(V_4)\,,\qquad \wr\!-\!O\!-\!V_d(V_1)_2(V_4)\,,$$

$$\wr\!-\!O\!-\!V_d(V_4)_2\,,\qquad \wr\!-\!O\!-\!V_e(V_1)_3(V_4)\,,\ \text{or}\ \wr\!-\!O\!-\!V_e(V_1)(V_4)_2$$

Wherein V_a, V_b, and V_1, are as described above; V_d is a pentavalent atom typically selected from P and N; V_e is a hexavalent atom typically S; and V_4 is a group bonded to V_a, V_b, V_d or V_e by a stable, double covalent bond, provided that at least one V_4 is =O, =S or =N-V_1, typically V_4, when other than =O, =S or =N-, is =C$(V_1)_2$ wherein V_1 is as described above.

Protecting groups for -OH functions (whether hydroxy, acid or other functions) are embodiments of "ether- or ester-forming groups".

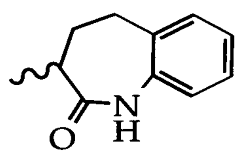
Particularly of interest are ether- or ester-forming groups that are capable of functioning as protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed under R_{6c} below. R_{6c} is capable of protecting hydroxyl or thio groups such that hydrolysis from the parental molecule yields hydroxyl or thio.

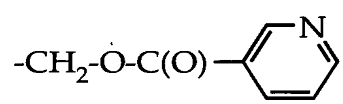
In its ester-forming role, R_{6a} typically is bound to any acidic group such as, by way of example and not limitation, a -CO_2H or -C(S)OH group, thereby resulting in -CO_2R_{6a}. R_{6a} for example is deduced from the enumerated ester groups of WO 95/07920.

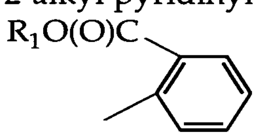
Examples of R_{6a} include

C_3-C_{12} heterocyle (described above) or C_6-C_{12} aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C_3-C_{12} heterocycle or C_6-C_{12} aryl substituted with halo, R_1, R_1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3-

and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-$N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl); 

; 

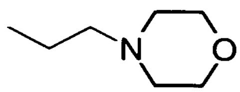
; 

; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2-CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl;

alkoxy ethyl [C_1-C_6 alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)];

alkyl substituted by any of the groups set forth above for aryl, in

particular OH or by 1 to 3 halo atoms (including $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CF_3$, and $-CH_2CCl_3$);


; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, $-CH_2-C(O)-N(R^1)_2$, $-CH_2-S(O)(R^1)$, $-CH_2-S(O)_2(R^1)$, $-CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1)$, cholesteryl, enolpyruvate ($HOOC-C(=CH_2)-$), glycerol;

a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., "Antimicrob. Agents Chemo." 5(6):670-671 [1974]);

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., "Chem. Pharm. Bull." 32(6)2241-2248 [1984]) where R_d is R_1, R_4 or aryl; and


;

The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO94/21604, or with isopropyl.

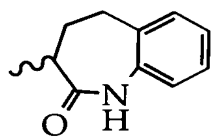
As further embodiments, Table A lists examples of R_{6a} ester moieties that for example can be bonded via oxygen to $-C(O)O-$ and $-P(O)(O-)_2$ groups. Several R_{6c} amidates also are shown, which are bound directly to $-C(O)-$ or $-P(O)_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-

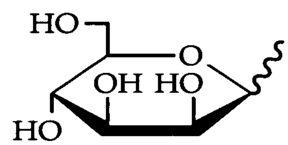
dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When W_1 is phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

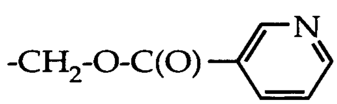
TABLE A

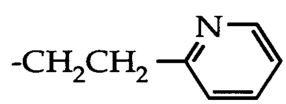
1. $-CH_2-C(O)-N(R_1)_2$	10. $-CH_2-O-C(O)-C(CH_3)_3$
2. $-CH_2-S(O)(R_1)$	11. $-CH_2-CCl_3$
3. $-CH_2-S(O)_2(R_1)$	12. $-C_6H_5$
4. $-CH_2-O-C(O)-CH_2-C_6H_5$	13. $-NH-CH_2-C(O)O-CH_2CH_3$
5. 3-cholesteryl	14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
6. 3-pyridyl	15. $-NHR_1$
7. N-ethylmorpholino	16. $-CH_2-O-C(O)-C_{10}H_{15}$
8. $-CH_2-O-C(O)-C_6H_5$	17. $-CH_2-O-C(O)-CH(CH_3)_2$
9. $-CH_2-O-C(O)-CH_2CH_3$	18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-(OC(O)CH_2R_1)$

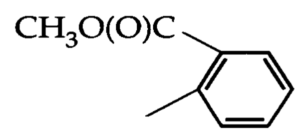
19. 

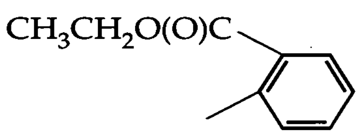
20. 

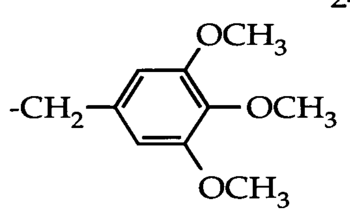
21. 

22. 

23. 

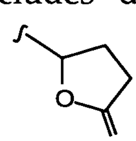
24. 

25. 

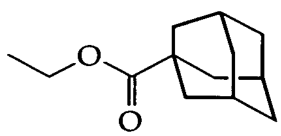
26. 

- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632,048.

R_{6a} also includes "double ester" forming profunctionalities such as $-CH_2OC(O)OCH_3$,  , $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R_1$ or $W_5)O((CO)R_{37})$ or $-CH(R_1$ or $W_5)((CO)OR_{38})$ (linked to oxygen of the acidic group) wherein R_{37} and R_{38} are alkyl, aryl, or alkylaryl groups (see U.S. patent 4,968,788). Frequently R_{37}

and R_{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful R_{6a} groups are alkylacyloxymethyl esters and their derivatives, including $-CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,



; $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, $-CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

As noted, R_{6a}, R_{6c} and R_{6b} groups optionally are used to prevent side reactions with the protected group during synthetic procedures, so they function as protecting groups (PRT) during synthesis. For the most part the decision as to which groups to protect, when to do so, and the nature of the PRT will be dependent upon the chemistry of the reaction to be protected against (e.g., acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect carboxyl, hydroxyl or amino groups. The order of deprotection to yield free groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

A very large number of R_{6a} hydroxy protecting groups and R_{6c} amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2,

Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For R_{6a} carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for W_1 acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

In some embodiments the R_{6a} protected acidic group is an ester of the acidic group and R_{6a} is the residue of a hydroxyl-containing functionality. In other embodiments, an R_{6c} amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical R_{6a} esters for protecting W_1 acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups W_1, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the W_1 acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical R_{6a} hydroxy protecting groups described in Greene (pages 14-118) include Ethers (Methyl); Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 35, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)); Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl, *t*-Butyl, Allyl, *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl); Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p*'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido); Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsily, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl); Esters

(Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate)); Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate); Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Niotro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chorodiphenylacetate, Isobutyrate, Monosuccinoate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

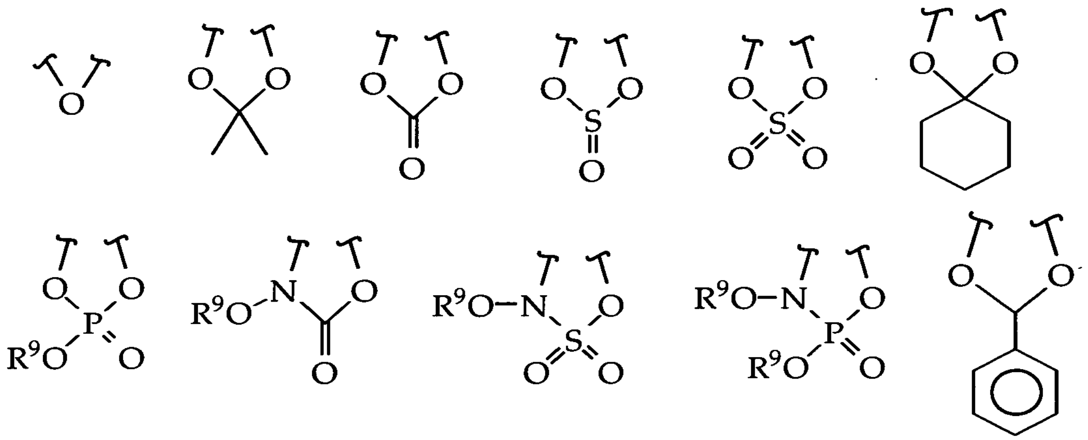
More typically, R_{6a} hydroxy protecting groups include substituted methyl ethers, substituted benzyl ethers, silyl ethers, and esters including sulfonic acid esters, still more typically, trialkylsilyl ethers, tosylates and acetates.

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the R_{6a} protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-

Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N*,*N*-Dimethylamino)ethylidene Derivative, α-(*N*,*N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

R_{6b} is H, a protecting group for amino or the residue of a carboxyl-containing compound, in particular H, -C(O)R_4, an amino acid, a polypeptide or a protecting group not -C(O)R_4, amino acid or polypeptide. Amide-forming R_{6b} are found for instance in group G_1. When R_{6b} is an amino acid or polypeptide it has the structure R_{15}NHCH(R_{16})C(O)-, where R_{15} is H, an amino acid or polypeptide residue, or R_5, and R_{16} is defined below.

R_{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R_{16} also is taken together with the amino acid α N to form a proline residue (R_{16} = -CH_2)$_3$-). However, R_{16} is generally the side group of a naturally-occurring amino acid such as H, -CH_3, -CH(CH_3)$_2$, -CH_2-CH(CH_3)$_2$, -$CHCH_3$-CH_2-CH_3, -CH_2-C_6H_5, -CH_2CH_2-S-CH_3, -CH_2OH, -CH(OH)-CH_3, -CH_2-SH, -CH_2-C_6H_4OH, -CH_2-CO-NH_2, -CH_2-CH_2-CO-NH_2, -CH_2-COOH, -CH_2-CH_2-COOH, -(CH_2)$_4$-NH_2 and -(CH_2)$_3$-NH-C(NH_2)-NH_2. R_{16} also includes 1-guanidinoprop-3-yl, benzyl, 4-

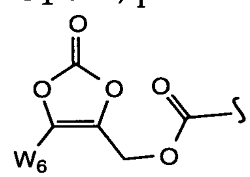
hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

R_{6b} are residues of carboxylic acids for the most part, but any of the typical amino protecting groups described by Greene at pages 315-385 are useful. They include Carbamates (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluoroenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-buthyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl); Substituted Ethyl (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl); Groups With Assisted Cleavage (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl); Groups Capable of Photolytic Cleavage (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl); Miscellaneous Carbamates (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl); Amides (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-

3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl); Amides With Assisted Cleavage (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one); Cyclic Imide Derivatives (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl); *N*-Alkyl and *N*-Aryl Amines (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide), Imine Derivatives (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene); Enamine Derivatives (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)); *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate); N-N Derivatives (*N*-nitro, *N*-nitroso, *N*-oxide); N-P Derivatives (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl); N-Si Derivatives; N-S Derivatives; N-Sulfenyl Derivatives (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-

pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R_1$ or $-N=CR_1N(R_1)_2$. Another protecting group, also usefull as a prodrug at the G_1 site, particularly for amino or $-NH(R_5)$, is:



see for example Alexander, J. et al., "J. Med. Chem." 39:480-486 (1996).

R_{6c} is H or the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R_4$, $NHC(O)R_4$, $-N(R_4)_2$, NH_2 or $-NH(R_4)(H)$, whereby for example the carboxyl or phosphonic acid groups of W_1 are reacted with the amine to form an amide, as in $-C(O)R_{6c}$, $-P(O)(R_{6c})_2$ or $-P(O)(OH)(R_{6c})$. In general, R_{6c} has the structure $R_{17}C(O)CH(R_{16})NH-$, where R_{17} is OH, OR_{6a}, OR_5, an amino acid or a polypeptide residue.

Amino acids are low molecular weight compounds, on the order of less than about 1,000 MW, that contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof.

Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline.

When R_{6b} and R_{6c} are single amino acid residues or polypeptides they usually are substituted at R_3, W_6, W_1 and/or W_2, but typically only W_1 or W_2. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example) and W_2. Similarly, conjugates are formed between W_1 and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of W_1 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R_{6a}, esterified with R_5 or amidated with R_{6c}. Similarly, the amino side chains R_{16} optionally will be blocked with R_{6b} or substituted with R_5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable in vivo or in vitro under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R_{6b} and R_{6c} include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β-hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β,β-dimethylaspartic acid, γ-hydroxyglutamic acid, β,γ-dihydroxyglutamic acid, β-phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β-aminoalanine, γ-aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α,α'-diaminosuccinic acid, α,α'-diaminoglutaric acid, α,α'-diaminoadipic acid, α,α'-diaminopimelic acid, α,α'-diamino-β-hydroxypimelic acid, α,α'-diaminosuberic acid, α,α'-diaminoazelaic acid, and α,α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1 - C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino-α-methyl-δ-hydroxyvaleric acid, α-amino-α-methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-

propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, tert-leucine, β-methyltryptophan and α-amino-β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β-hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, γ-hydroxynorvaline, δ-hydroxynorvaline and epsilon-hydroxynorleucine residues; canavine and canaline; γ-hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β–thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dicloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α-hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of

one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In embodiments where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate

peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as R_{6b} or R_{6c}. When W_1 is phosphonate, the sequence -X4-pro-X5- (where X4 is any amino acid residue and X5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter

found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., "Pharm Res." 9:969-978 (1992). Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N (EC 3.4.11.2). In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A (EC 3.4.11.7), di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase 24.11 (EC 3.4.24.11), and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P (EC 3.4.17). Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

Stereoisomers

The compounds of the invention are enriched or resolved optical isomers at any or all asymmetric atoms. For example, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diasteromeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention.

One or more of the following enumerated methods are used to prepare the enantiomerically enriched or pure isomers herein. The methods are listed in approximately their order of preference, i.e., one ordinarily should employ stereospecific synthesis from chriral precursors before chromatographic resolution before spontaneous crystallization.

Stereospecific synthesis is described below. Methods of this type

conveniently are used when the appropriate chiral starting material is available and reaction steps are chosen do not result in undesired racemization at chiral sites. One advantage of stereospecific synthesis is that it does not produce undesired enantiomers that must be removed from the final product, thereby lowering overall synthetic yield. In general, those skilled in the art would understand what starting materials and reaction conditions should be used to obtain the desired enantiomerically enriched or pure isomers by stereospecific synthesis. If an unexpected racemization occurs in a method thought to be stereospecific then one needs only to use one of the following separation methods to obtain the desired product.

If a suitable stereospecific synthesis cannot be empirically designed or determined with routine experimentation then those skilled in the art would turn to other methods. One method of general utility is chromotographic resolution of enantiomers on chiral chromatography resins. These resins are packed in columns, commonly called Pirkle columns, and are commercially available. The columns contain a chiral stationary phase. The racemate is placed in solution and loaded onto the column, and thereafter separated by HPLC. See for example, Proceedings Chromatographic Society - International Symposium on Chiral Separations, Sept. 3-4, 1987. Examples of chiral columns that could be used to screen for the optimal separation technique would include Diacel Chriacel OD, Regis Pirkle Covalent Dphenylglycine, Regis Pirkle Type 1A, Astec Cyclobond II, Astec Cyclobond III, Serva Chiral D-DL=Daltosil 100, Bakerbond DNBLeu, Sumipax OA-1000, Merck Cellulose Triacetate column, Astec Cyclobond I-Beta, or Regis Pirkle Covalent D-Naphthylalanine. Not all of these columns are likely to be effective with every racemic mixture. However, those skilled in the art understand that a certain amount of routine screening may be required to identify the most effective stationary phase. When using such columns it is desireable to employ embodiments of the compounds of this invention in which the charges are not neutralized, e.g., where acidic functionalities such as carboxyl are not esterified or amidated.

Another method entails converting the enantiomers in the mixture to diasteriomers with chiral auxiliaries and then separting the conjugates by ordinary column chromatography. This is a very suitable method, particularly when the embodiment contains free carboxyl, amino or hydroxyl that will form a salt or covalent bond to a chiral auxiliary. Chirally pure

amino acids, organic acids or organosulfonic acids are all worthwhile exploring as chiral auxiliaries, all of which are well known in the art. Salts with such auxiliaries can be formed, or they can be covalently (but reversibly) bonded to the functional group. For example, pure D or L amino acids can be used to amidate the carboxyl group of embodiments of this invention and then separated by chromatography.

Enzymatic resolution is another method of potential value. In such methods one prepares covalent derivatives of the enantiomers in the racemic mixture, generally lower alkyl esters (for example of carboxyl), and then exposes the derivative to enzymatic cleavage, generally hydrolysis. For this method to be successful an enzyme must be chosen that is capable of stereospecific cleavage, so it is frequently necessary to routinely screen several enzymes. If esters are to be cleaved, then one selects a group of esterases, phosphatases, and lipases and determines their activity on the derivative. Typical esterases are from liver, pancreas or other animal organs, and include porcine liver esterase.

If the enatiomeric mixture separates from solution or a melt as a conglomerate, i.e., a mixture of enantiomerically-pure crystals, then the crystals can be mechanically separated, thereby producing the enantiomerically enriched preparation. This method, however, is not practical for large scale preparations and is of no value for true racemic compounds.

Asymmetric synthesis is another technique for achieving enantiomeric enrichment. For example, a chiral protecting group is reacted with the group to be protected and the reaction mixture allowed to equilibrate. If the reaction is enantiomerically specific then the product will be enriched in that enantiomer.

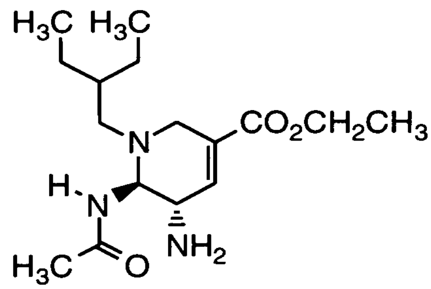
Further guidance in the separation of enantiomeric mixtures can be found, by way of example and not limitation, in "Enantiomers, Racemates, and resolutions", Jean Jacques, Andre Collet, and Samuel H. Wilen (Krieger Publishing Company, Malabar, FL, 1991, ISBN 0-89464-618-4). In particular, Part 2, Resolution of Enantiomer Mixture, pages 217-435; more particularly, section 4, Resolution by Direct Crystallization, pages 217-251, section 5, Formation and Separation of Diastereomers, pages 251-369, section 6, Crystallization-Induced Asymmetric Transformations, pages 369-378, and section 7, Experimental Aspects and Art of Resolutions, pages 378-435; still

more particularly, section 5.1.4, Resolution of Alcohols, Transformation of Alcohols into Salt-Forming Derivatives, pages 263-266, section 5.2.3, Covalent Derivatives of Alcohols, Thiols, and Phenols, pages 332-335, section 5.1.1, Resolution of Acids, pages 257-259, section 5.1.2, Resolution of Bases, pages 259-260, section 5.1.3, Resolution of Amino Acids, page 261-263, section 5.2.1, Covalent Derivatives of Acids, page 329, section 5.2.2, Covalent derivatives of Amines, pages 330-331, section 5.2.4, Covalent Derivatives of Aldehydes, Ketones, and Sulfoxides, pages 335-339, and section 5.2.7, Chromatographic Behavior of Covalent Diastereomers, pages 348-354, are cited as examples of the skill of the art.

The compounds of the invention can also exist as tautomeric isomers in certain cases. For example, ene-amine tautomers can exist for imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

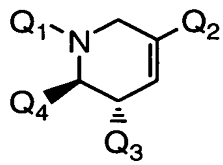
Exemplary Enumerated Compounds.

By way of example and not limitation, embodiment compounds are named below in tabular format (Table 6). Generally, each compound is depicted as a substituted nucleus in which the nucleus is designated by capital letter and each substituent is designated in order by lower case letter or number. Table 1 are a schedule of nuclei which differ principally by the position of ring unsaturation and the nature of ring substituents. Each nucleus is given a alphabetical designation from Table 1, and this designation appears first in each compound name. Similarly, Tables 2a-al, 3a-b, 4a-c, and 5a-d list the selected Q_1, Q_2, Q_3 and Q_4 substituents, again by letter or number designation. Accordingly, each named compound will be depicted by a capital letter designating the nucleus from Table 1, followed by a number designating the Q_1 substituent, a lower case letter designating the Q_2 substituent, a number designating the Q_3 substituent, and a lower case letter or letters designating the Q_4 substituent. Thus, the structure below has the name shown.

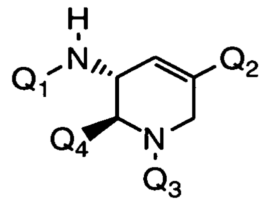


A.141.x.4.i

Table 1

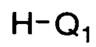


A

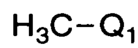


B

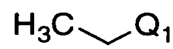
Table 2a



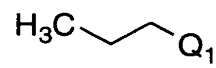
1



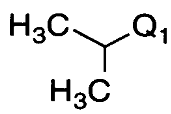
2



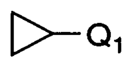
3



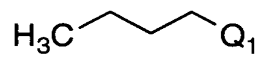
4



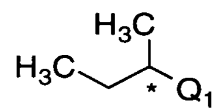
5



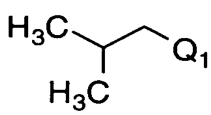
6



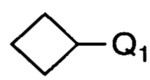
7



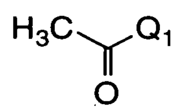
8



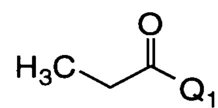
9



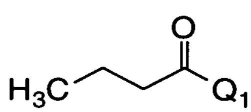
10



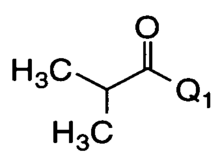
11



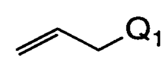
12



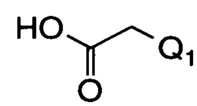
13



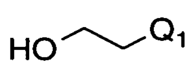
14



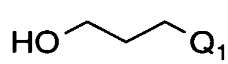
15



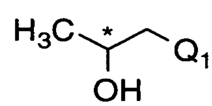
16



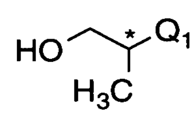
17



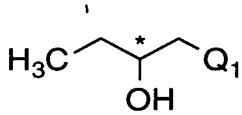
18



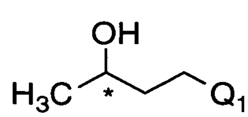
19



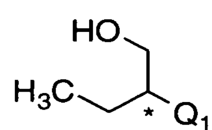
20



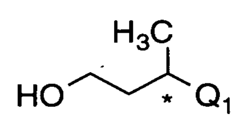
21



22

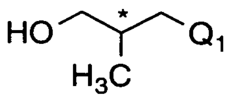


23

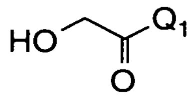


24

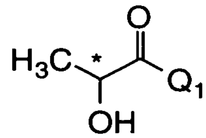
Table 2b



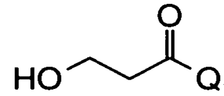
25



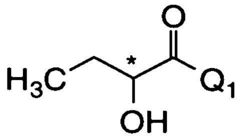
26



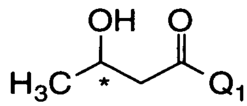
27



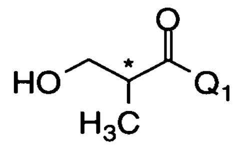
28



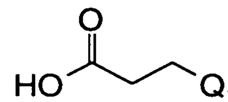
29



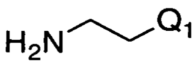
30



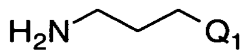
31



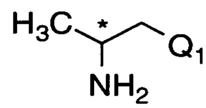
32



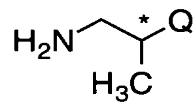
33



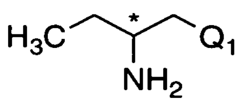
34



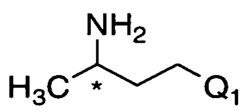
35



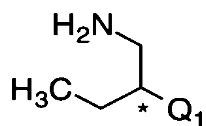
36



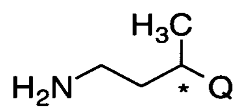
37



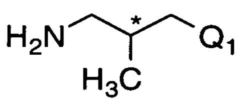
38



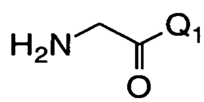
39



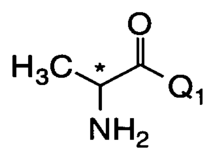
40



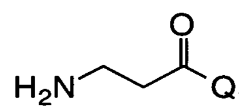
41



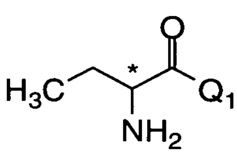
42



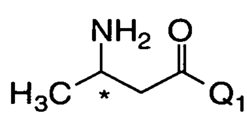
43



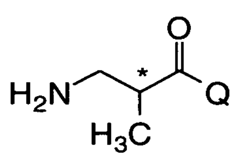
44



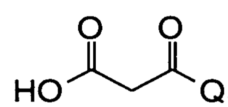
45



46

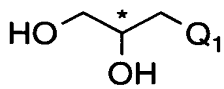


47

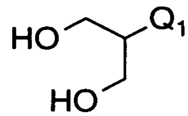


48

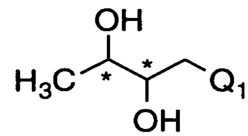
Table 2c



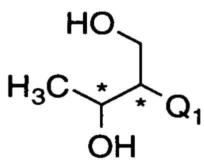
49



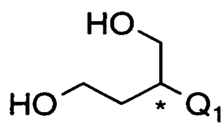
50



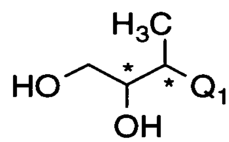
51



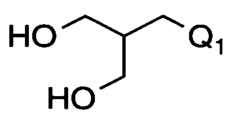
52



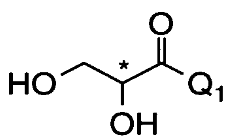
53



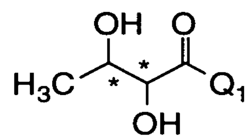
54



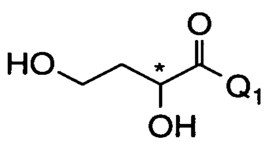
55



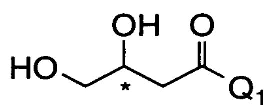
56



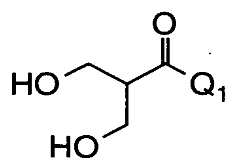
57



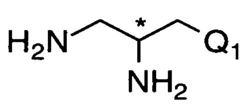
58



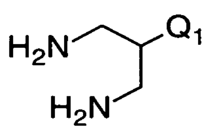
59



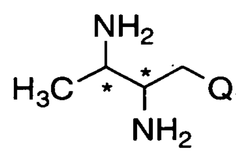
60



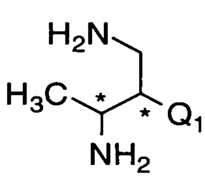
61



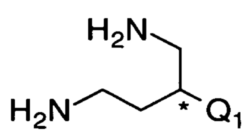
62



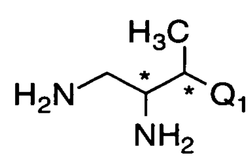
63



64

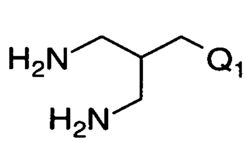


65

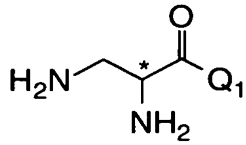


66

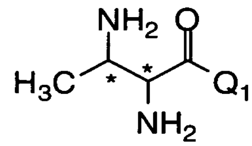
Table 2d



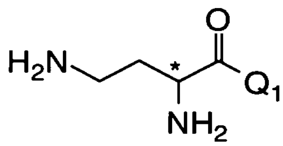
67



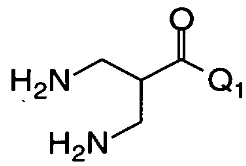
68



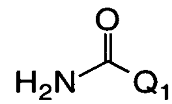
69



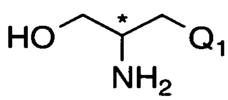
70



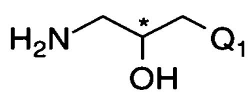
71



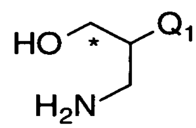
72



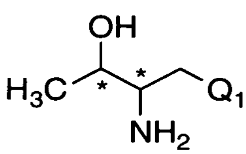
73



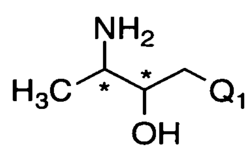
74



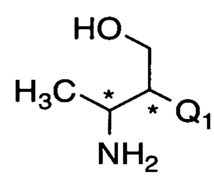
75



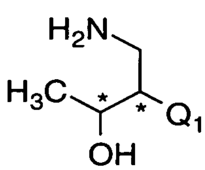
76



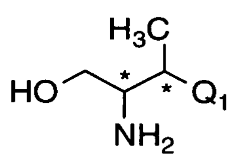
77



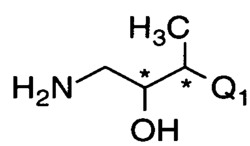
78



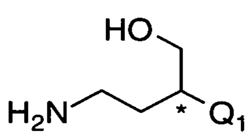
79



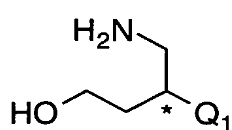
80



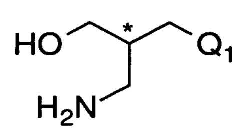
81



82

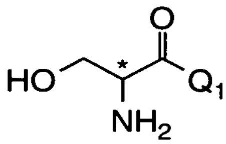


83

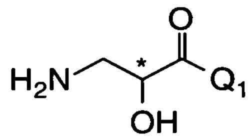


84

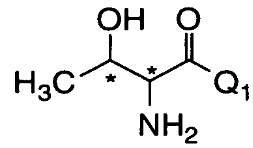
Table 2e



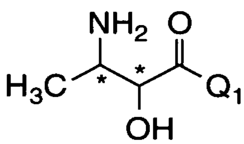
85



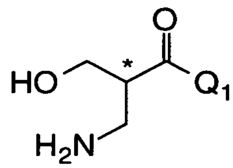
86



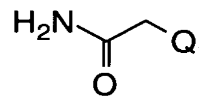
87



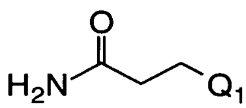
88



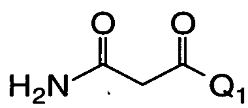
89



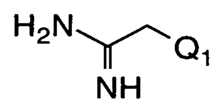
90



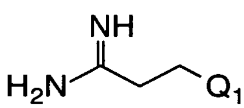
91



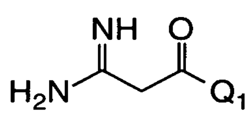
92



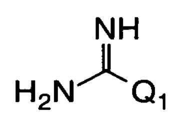
93



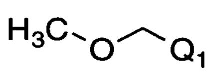
94



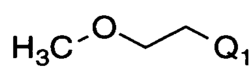
95



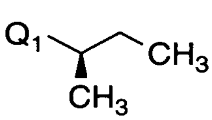
96



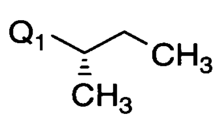
97



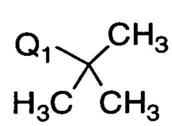
98



100

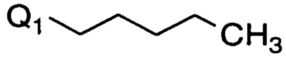


101

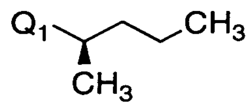


102

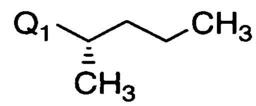
Table 2f



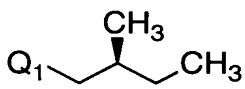
103



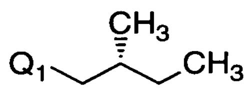
104



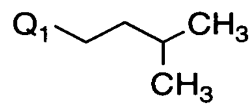
105



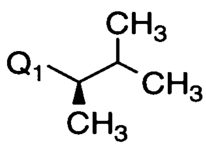
106



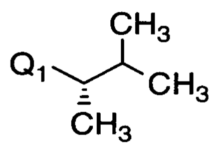
107



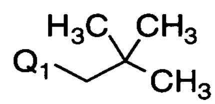
108



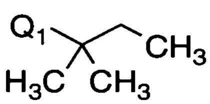
109



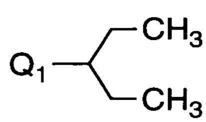
110



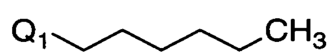
111



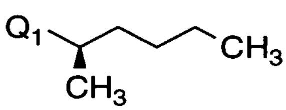
112



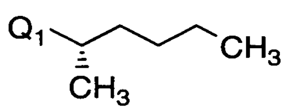
113



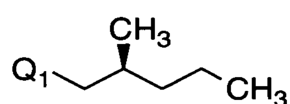
114



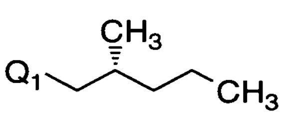
115



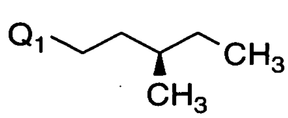
116



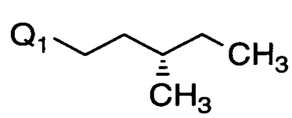
117



118

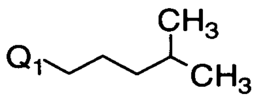


119

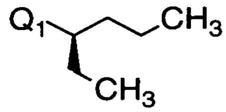


120

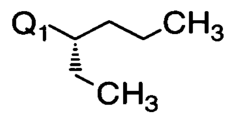
Table 2g



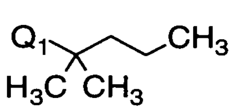
121



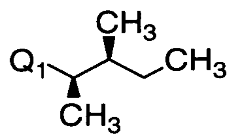
122



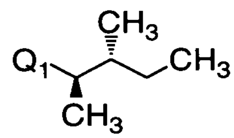
123



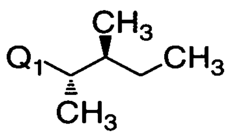
124



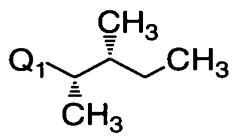
125



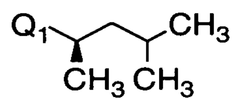
126



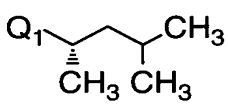
127



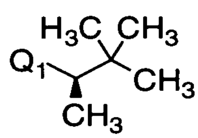
128



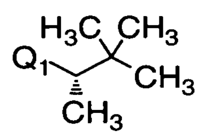
129



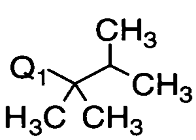
130



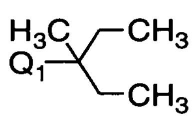
131



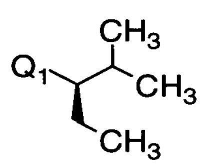
132



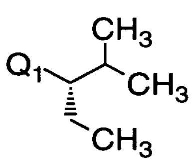
133



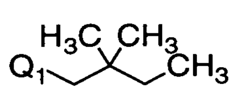
134



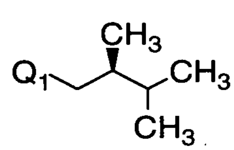
135



136

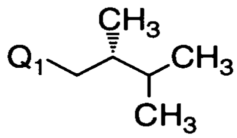


137

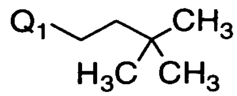


138

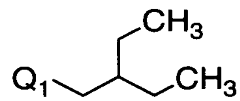
Table 2h



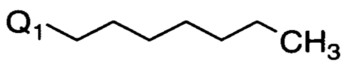
139



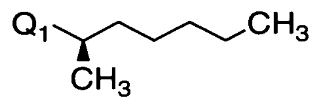
140



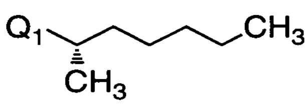
141



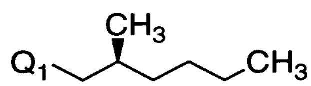
142



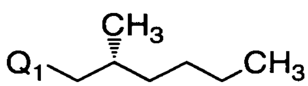
143



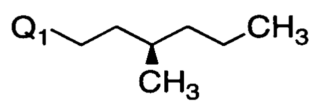
144



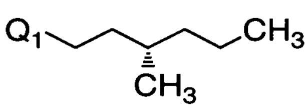
145



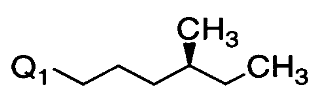
146



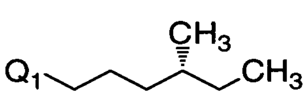
147



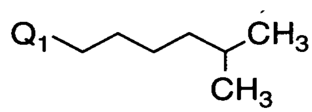
148



149

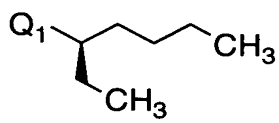


150

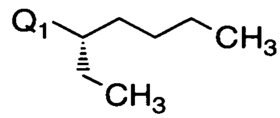


151

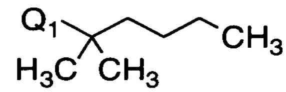
Table 2i



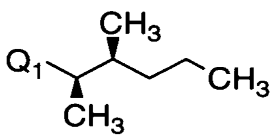
152



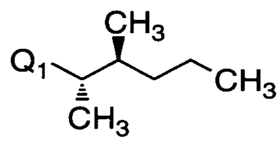
153



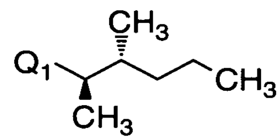
154



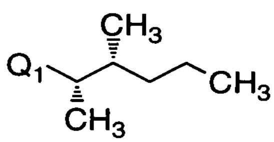
155



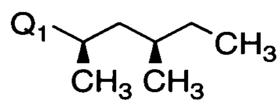
156



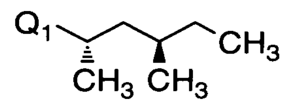
157



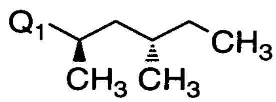
158



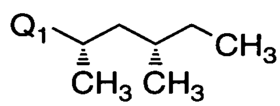
159



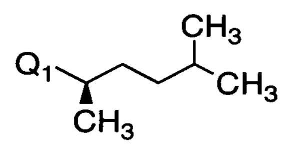
160



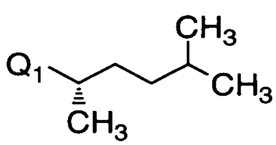
161



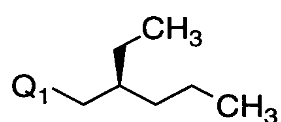
162



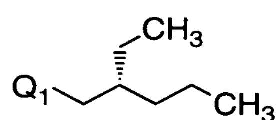
163



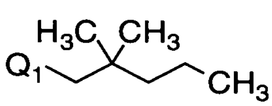
164



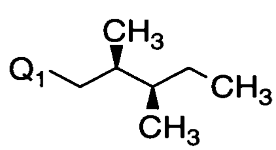
165



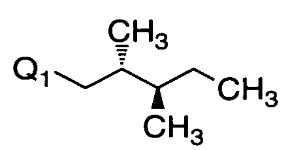
166



167

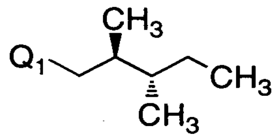


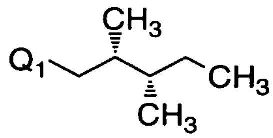
168

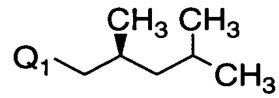


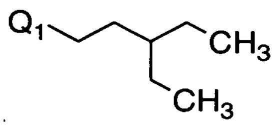
169

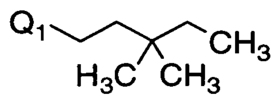
Table 2j

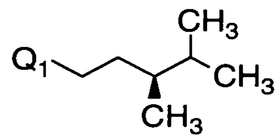

170

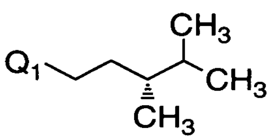

171

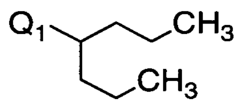

172

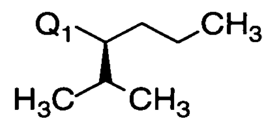

173

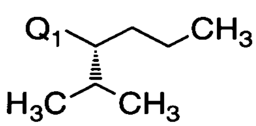

174

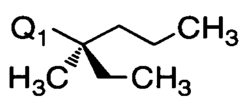

175

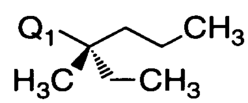

176

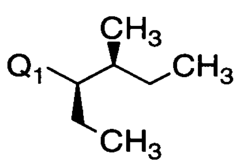

177

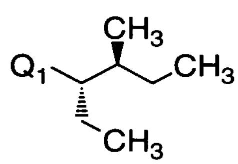

178

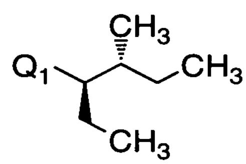

179

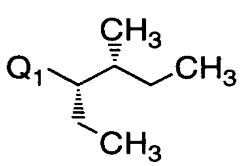

180

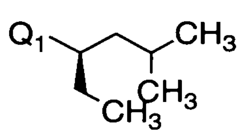

181


182


183


184


185


186

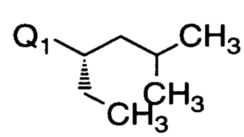
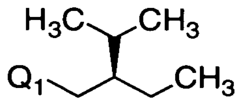
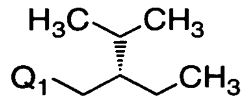

187

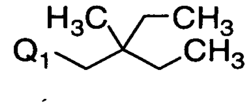
Table 2k



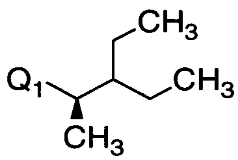
188



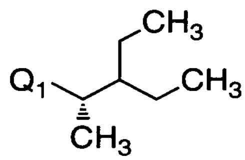
189



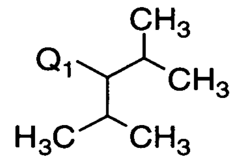
190



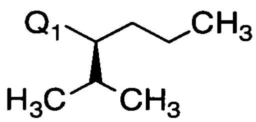
191



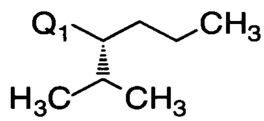
192



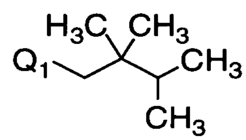
193



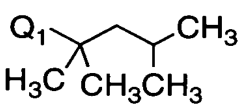
194



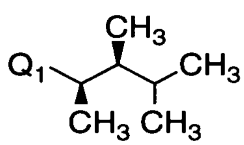
195



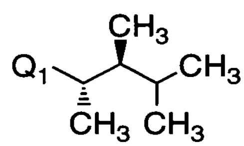
196



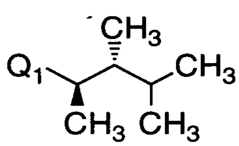
197



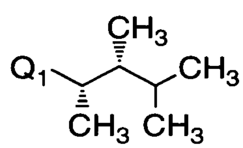
198



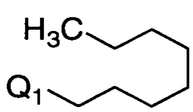
199



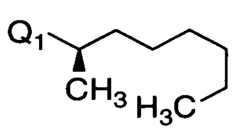
200



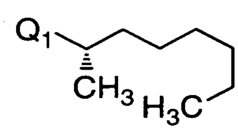
201



202

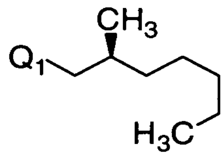


203

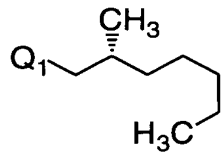


204

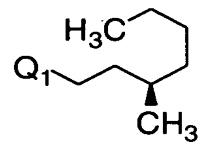
Table 2l



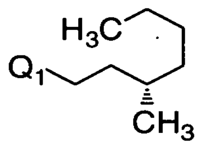
205



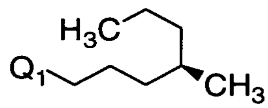
206



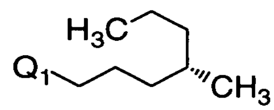
207



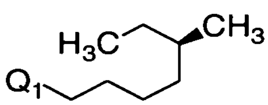
208



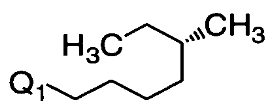
209



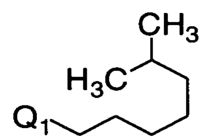
210



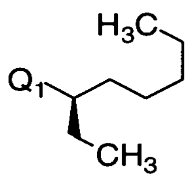
211



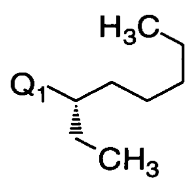
212



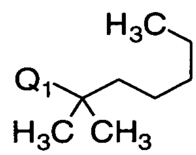
213



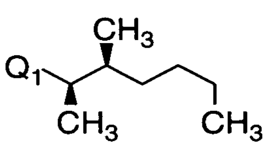
214



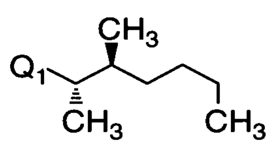
215



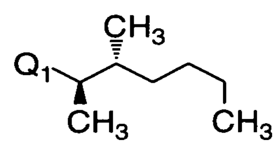
216



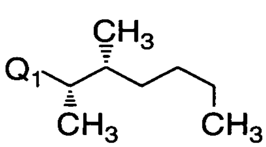
217



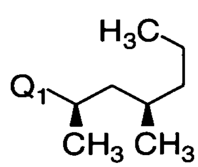
218



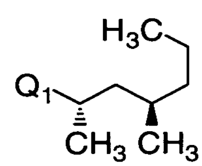
219



220

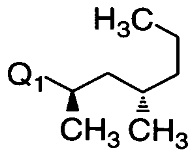


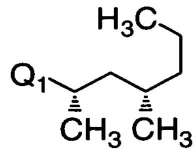
221

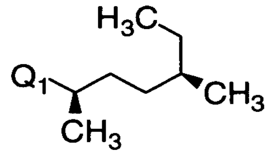


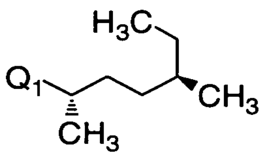
222

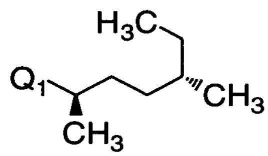
Table 2m

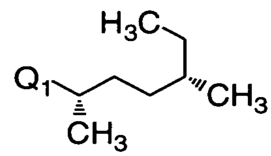

223

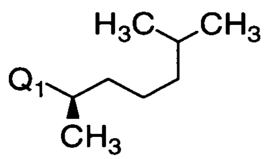

224

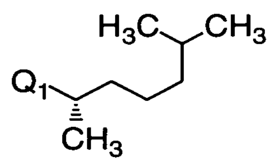

225

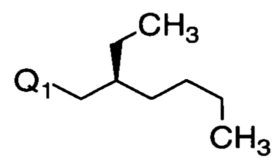

226

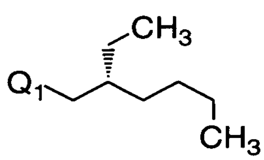

227


228

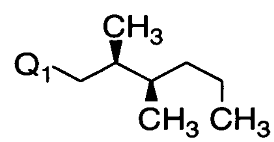

229

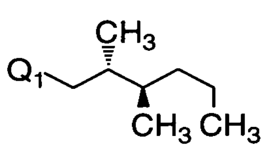

230

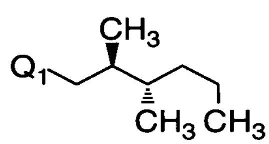

231

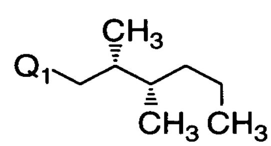

232

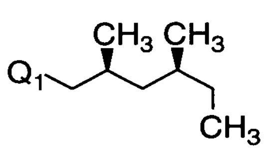

233

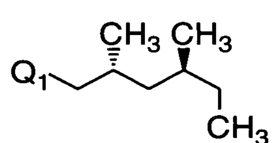

234


235


236


237


238


239

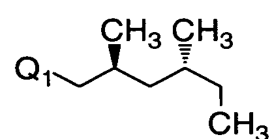
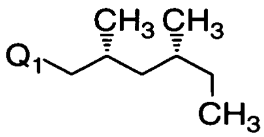
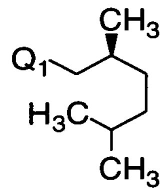

240

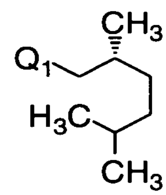
Table 2n



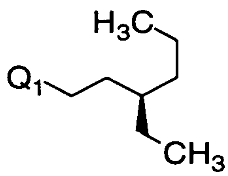
241



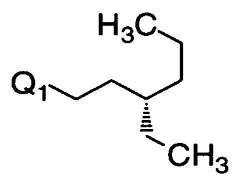
242



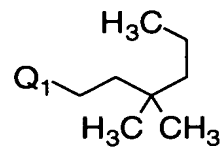
243



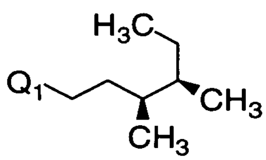
244



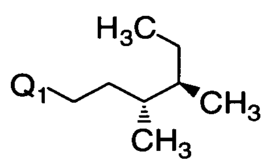
245



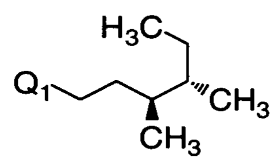
246



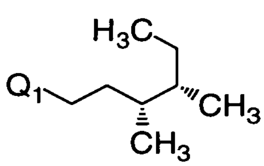
247



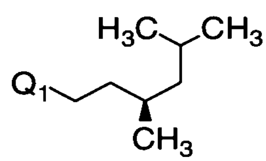
248



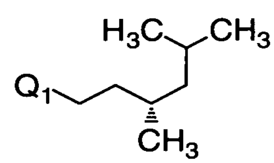
249



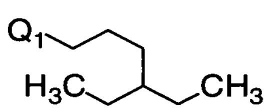
250



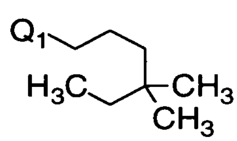
251



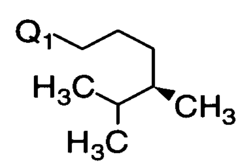
252



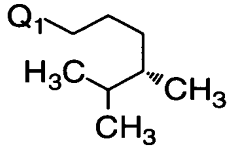
253



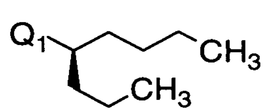
254



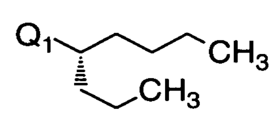
255



256

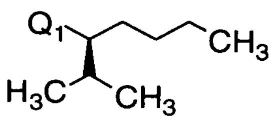


257

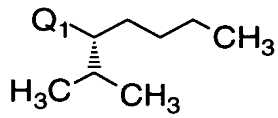


258

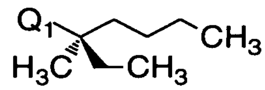
Table 2o



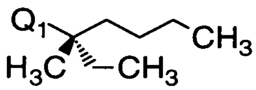
259



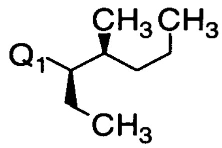
260



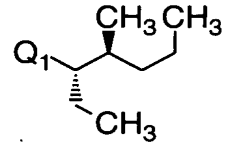
261



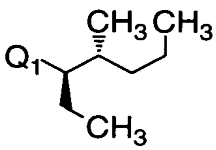
262



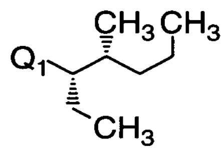
263



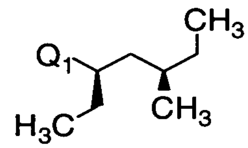
264



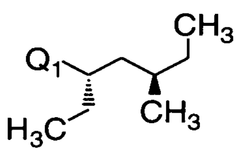
265



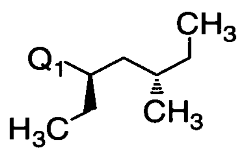
266



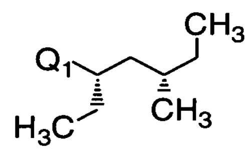
267



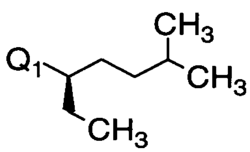
268



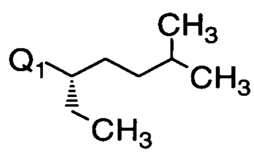
269



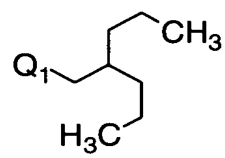
270



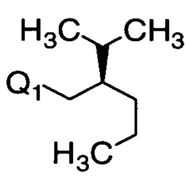
271



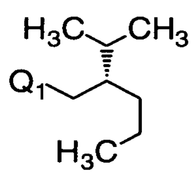
272



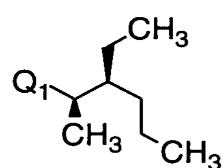
273



274

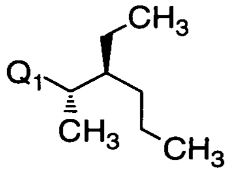


275

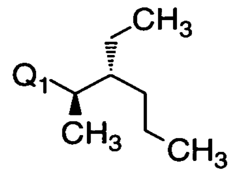


276

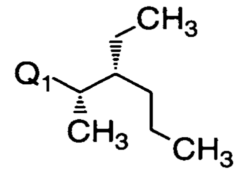
Table 2p



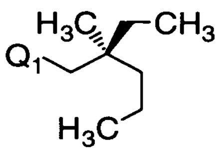
277



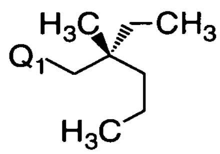
278



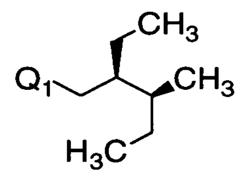
279



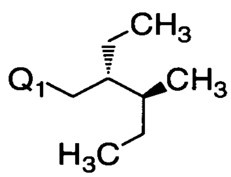
280



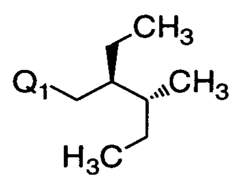
281



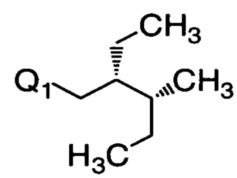
282



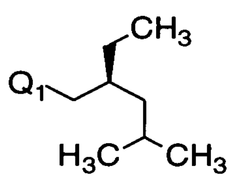
283



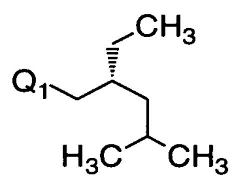
284



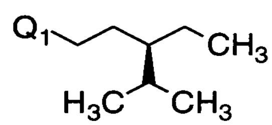
285



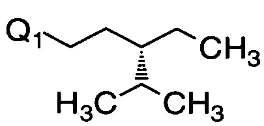
286



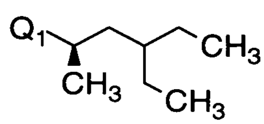
287



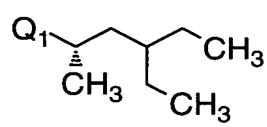
288



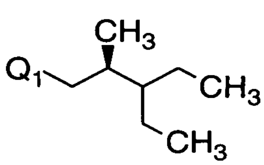
289



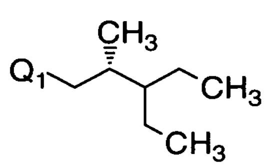
290



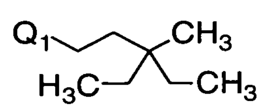
291



292

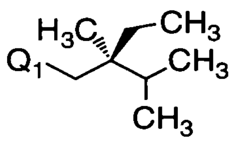


293

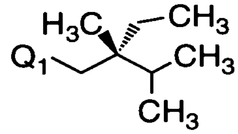


294

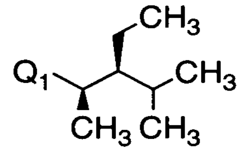
Table 2q



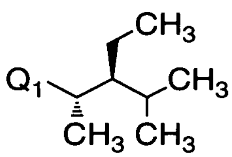
295



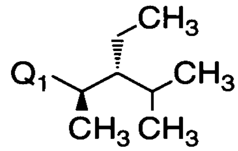
296



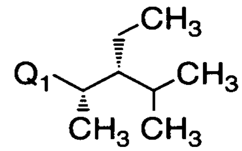
297



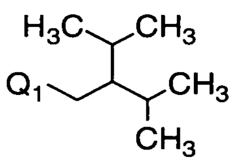
298



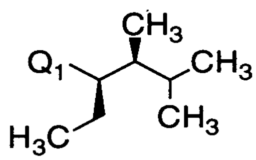
299



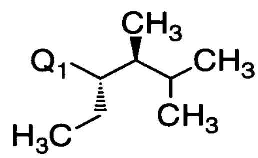
300



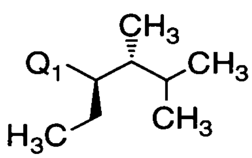
301



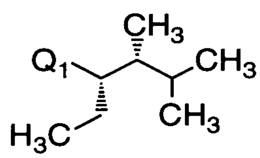
302



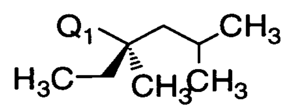
303



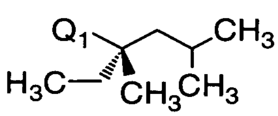
304



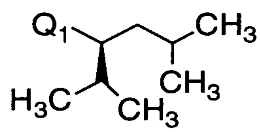
305



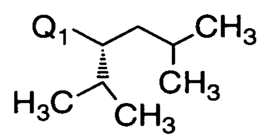
306



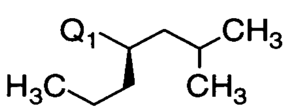
307



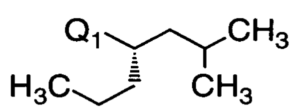
308



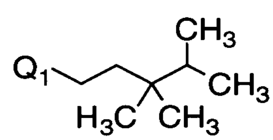
309



310

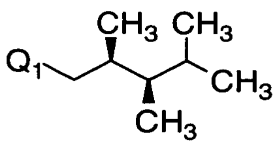


311

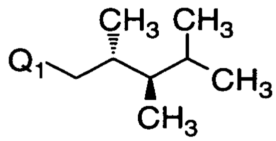


312

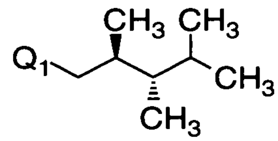
Table 2r



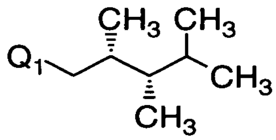
313



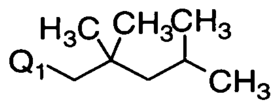
314



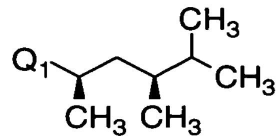
315



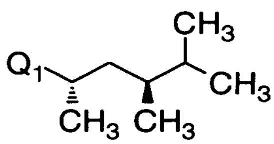
316



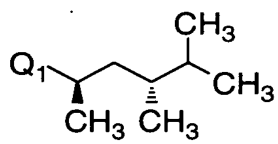
317



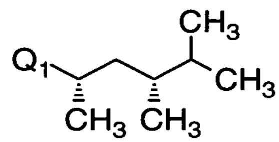
318



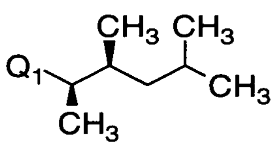
319



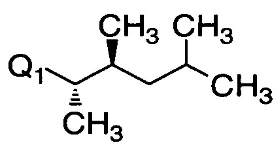
320



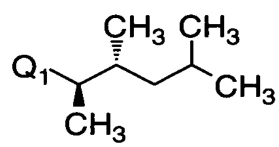
321



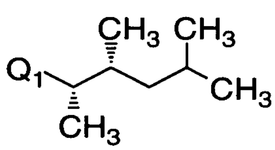
322



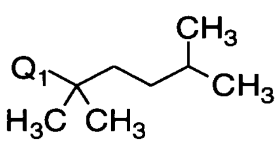
323



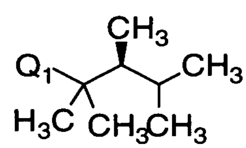
324



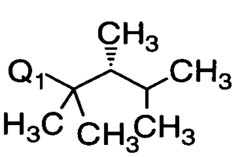
325



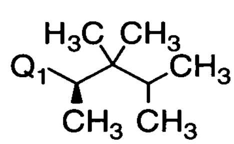
326



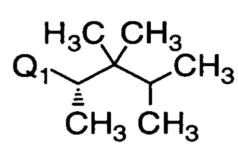
327



328

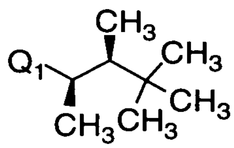


329

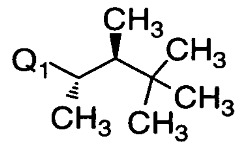


330

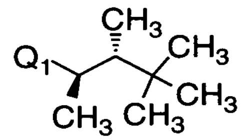
Table 2s



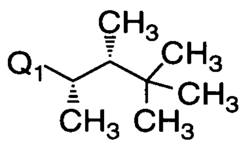
331



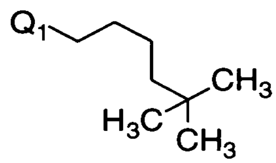
332



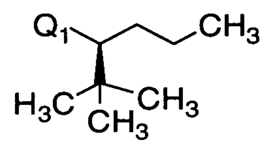
333



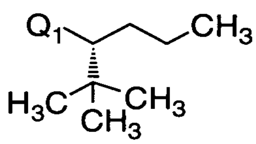
334



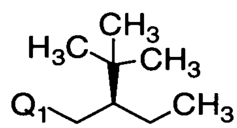
335



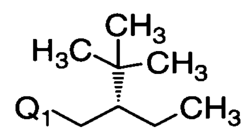
336



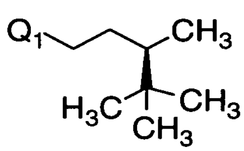
337



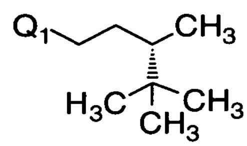
338



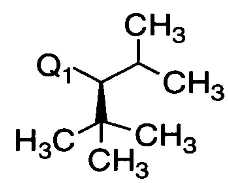
339



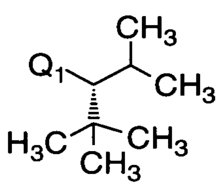
340



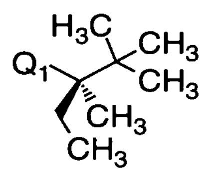
341



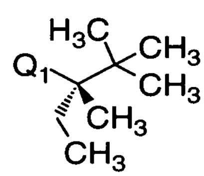
342



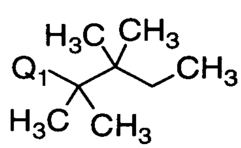
343



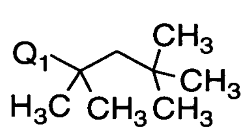
344



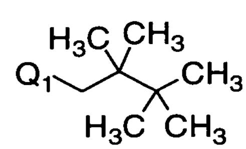
345



346

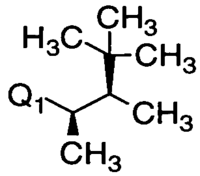


347

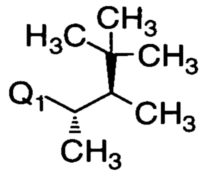


348

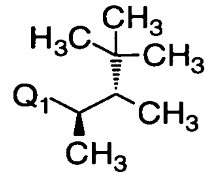
Table 2t



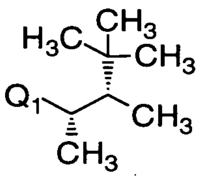
349



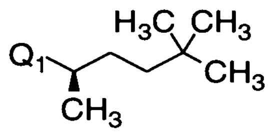
350



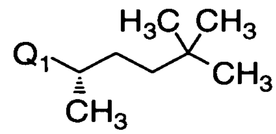
351



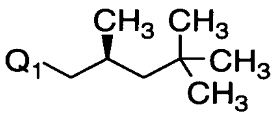
352



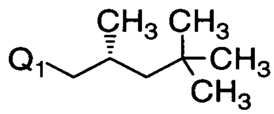
353



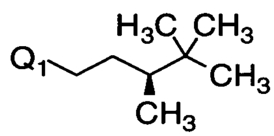
354



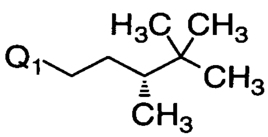
355



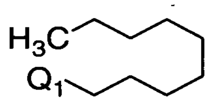
356



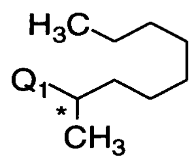
357



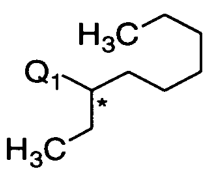
358



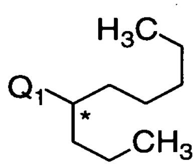
359



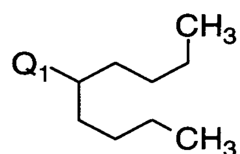
360



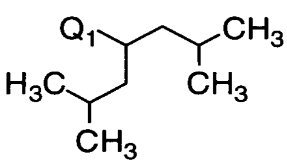
361



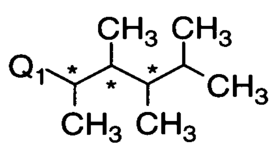
362



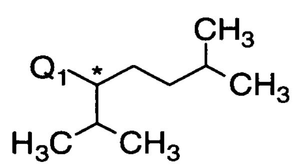
363



364

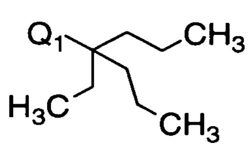


365

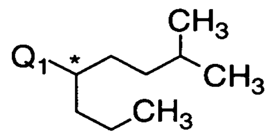


366

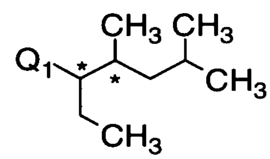
Table 2u



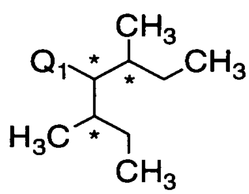
367



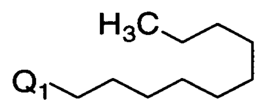
368



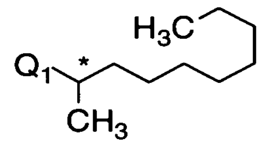
369



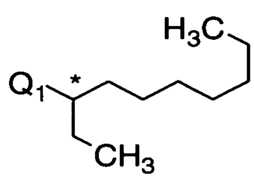
370



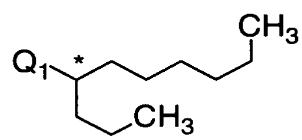
371



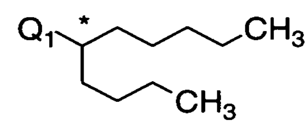
372



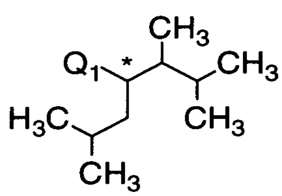
373



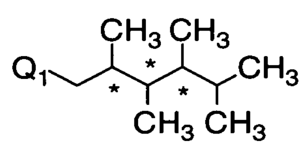
374



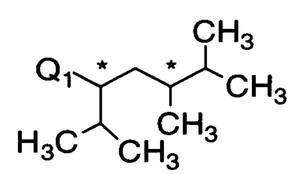
375



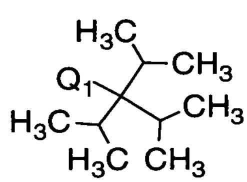
376



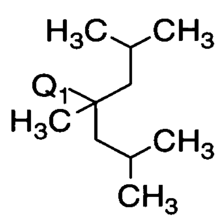
377



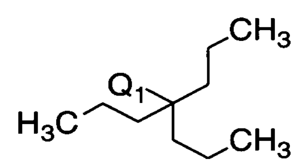
378



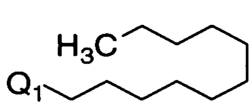
379



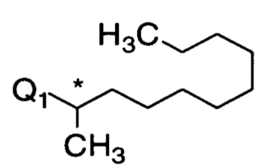
380



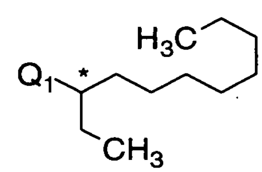
381



382

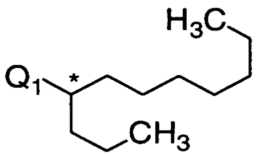


383

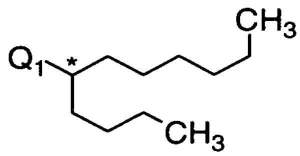


384

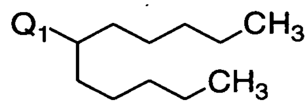
Table 2v



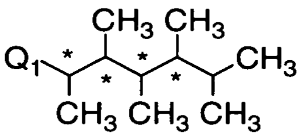
385



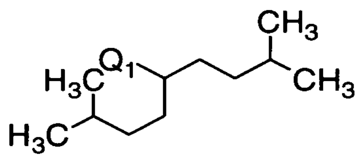
386



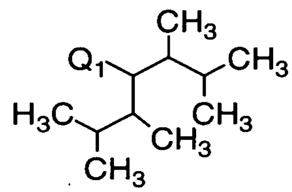
387



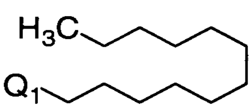
388



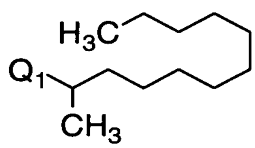
389



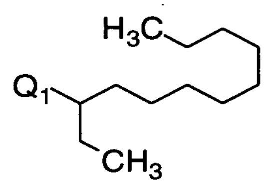
390



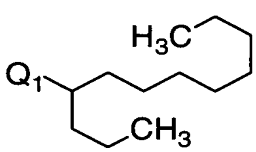
391



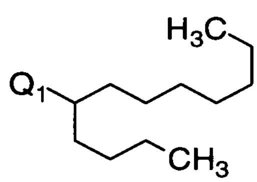
392



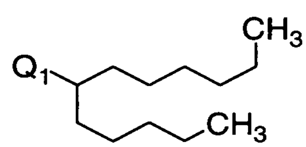
393



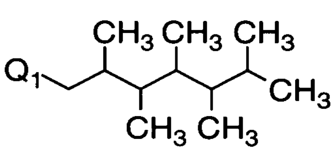
394



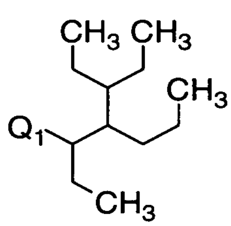
395



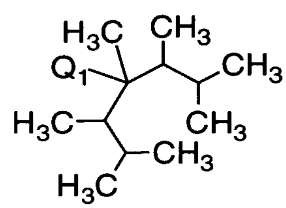
396



397

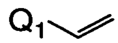


398

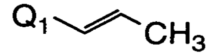


399

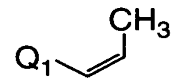
Table 2w



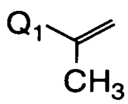
400



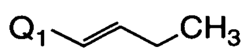
401



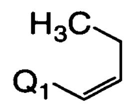
402



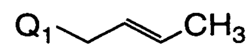
403



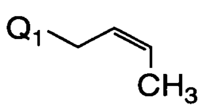
404



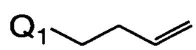
405



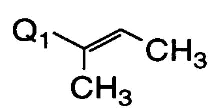
406



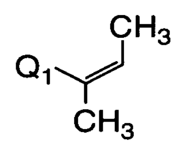
407



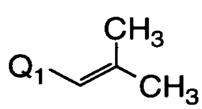
408



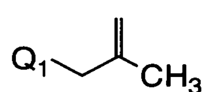
409



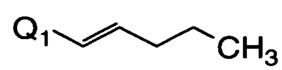
410



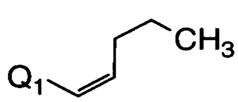
411



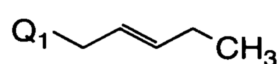
412



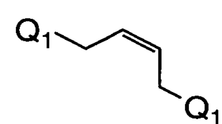
413



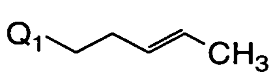
414



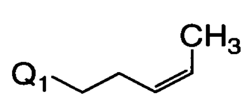
415



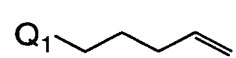
416



417

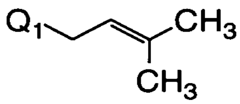


418

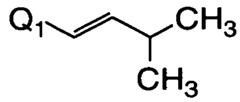


419

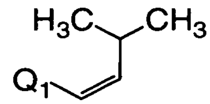
Table 2x



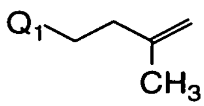
420



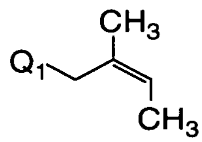
421



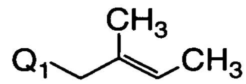
422



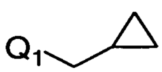
423



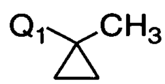
424



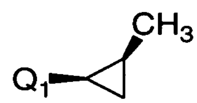
425



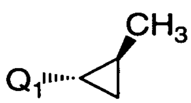
426



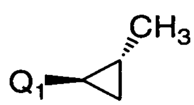
427



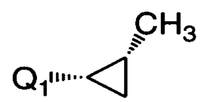
428



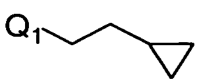
429



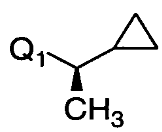
430



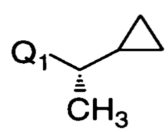
431



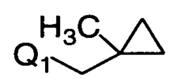
432



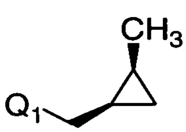
433



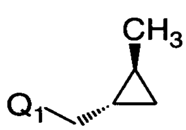
434



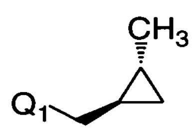
435



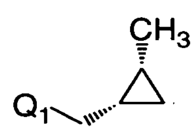
436



437

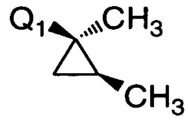


438

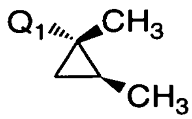


439

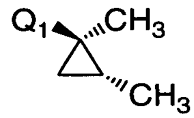
Table 2y



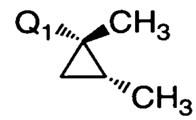
440



441



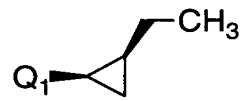
442



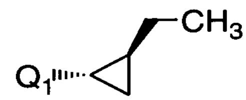
443

444

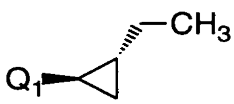
445



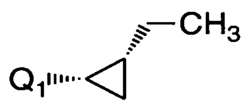
446



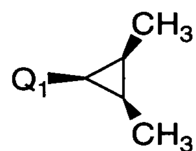
447



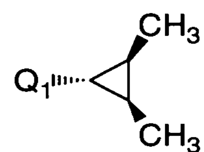
448



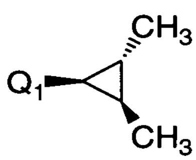
449



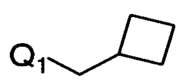
450



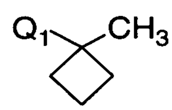
451



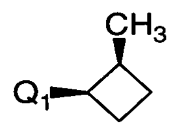
452



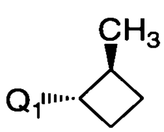
453



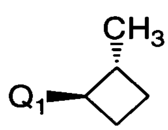
454



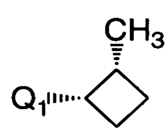
455



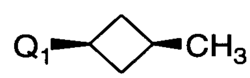
456



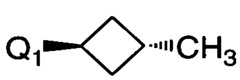
457



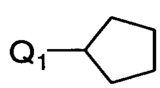
458



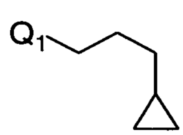
459



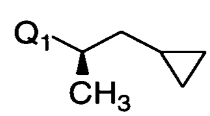
460



461

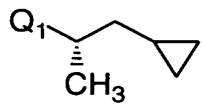


462

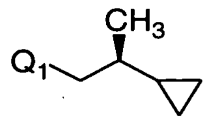


666

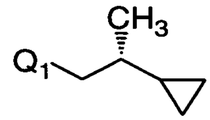
Table 2z



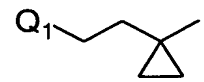
463



464



465

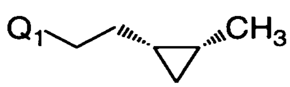


466

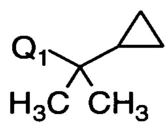
467

468

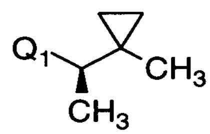
469



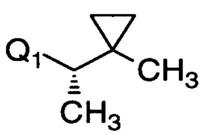
470



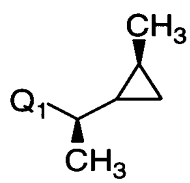
471



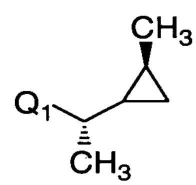
472



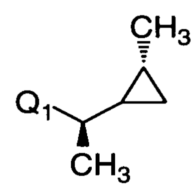
473



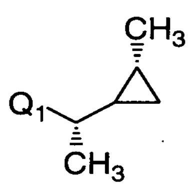
474



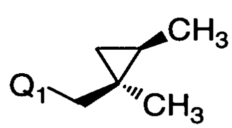
475



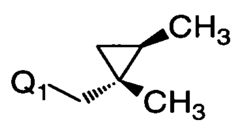
476



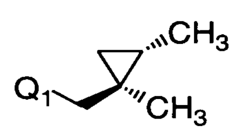
477



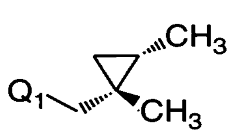
478



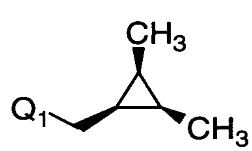
479



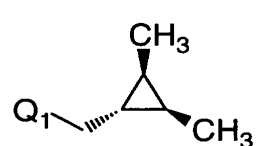
480



481

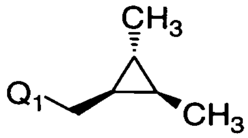


482

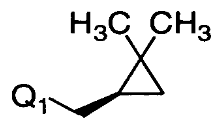


483

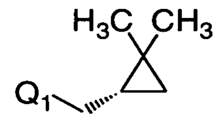
Table 2aa



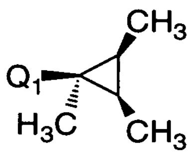
484



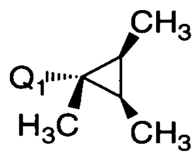
485



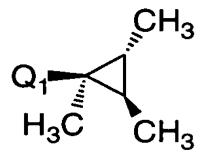
486



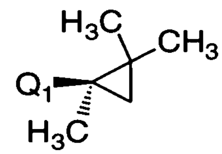
487



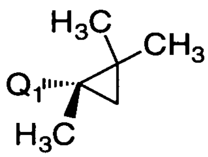
488



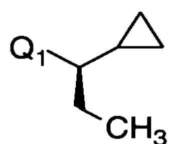
489



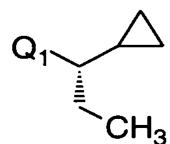
490



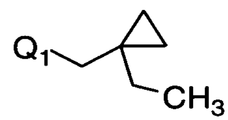
491



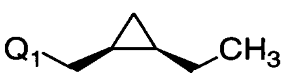
492



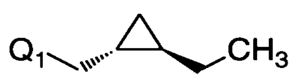
493



494



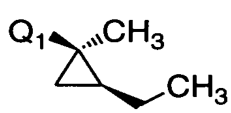
495



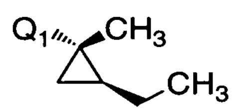
496

497

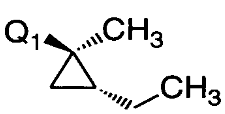
498



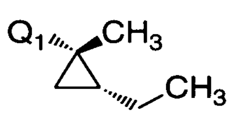
499



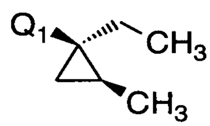
500



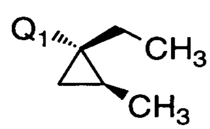
501



502

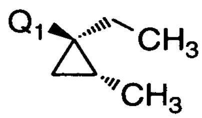


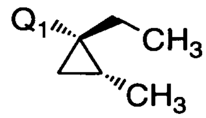
503

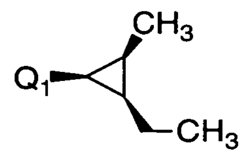


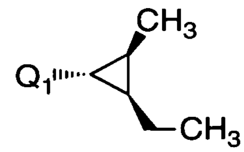
504

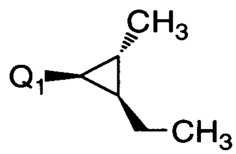
Table 2ab

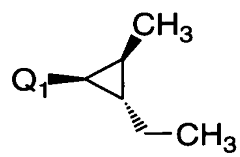

505

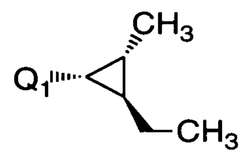

506

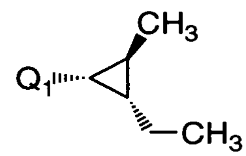

507

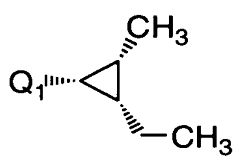

508

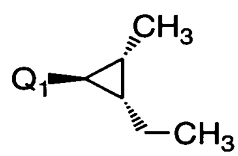

509

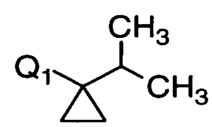

510

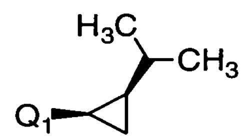

511

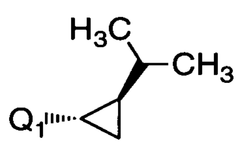

512

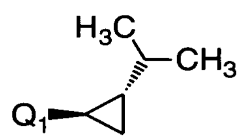

513

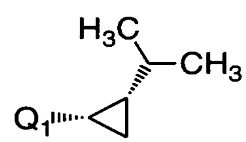

514

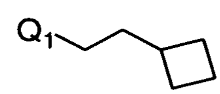

515

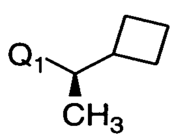

516

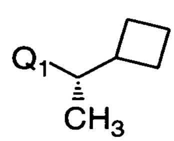

517

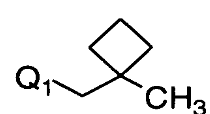

518

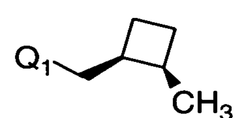

519

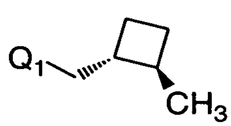

520

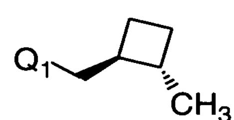

521


522


523


524


525


526

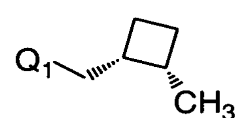
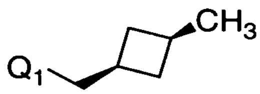
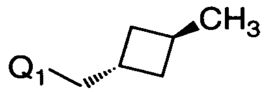

527

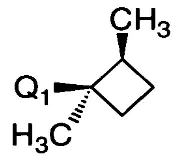
Table 2ac



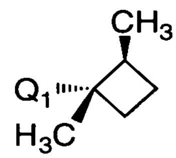
528



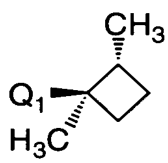
529



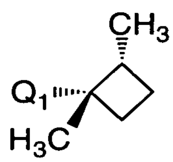
530



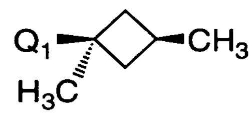
531



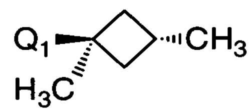
532



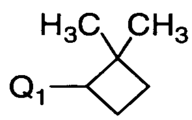
533



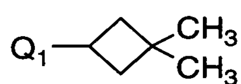
534



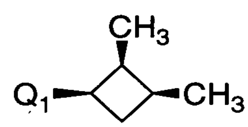
535



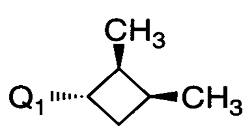
536



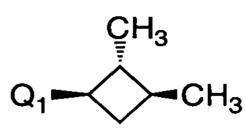
537



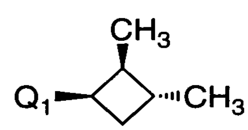
538



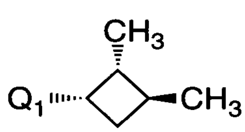
539



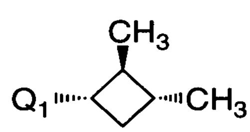
540



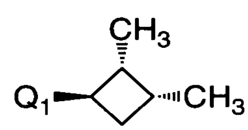
541



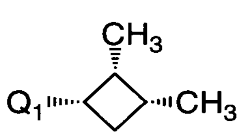
542



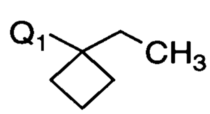
543



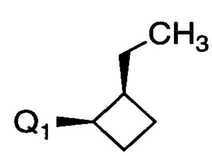
544



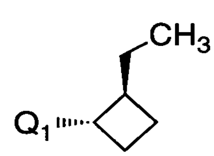
545



546

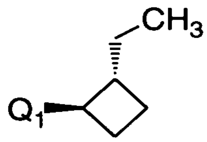


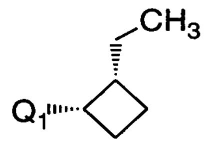
547

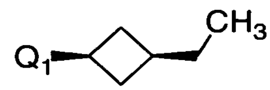


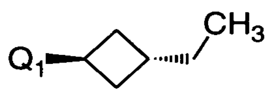
548

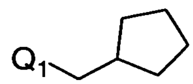
Table 2ad

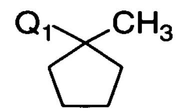

549

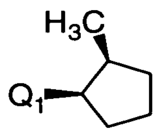

550

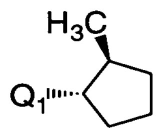

551

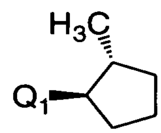

552

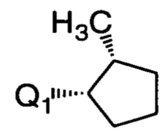

553

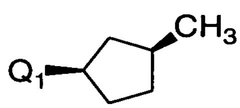

554

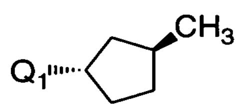

555

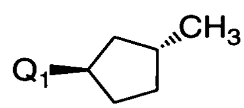

556

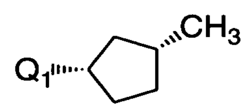

557

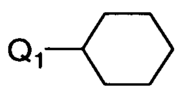

558

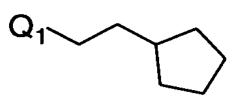

559

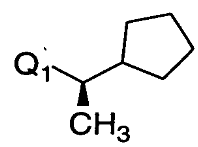

560

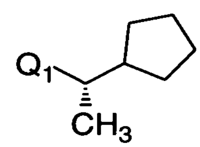

561

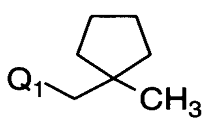

562

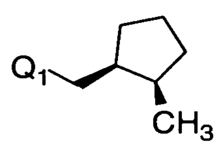

563


564


565


566


567


568

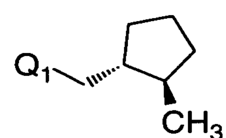
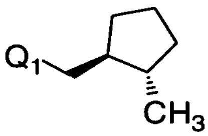
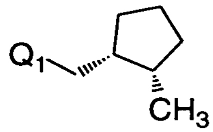

569

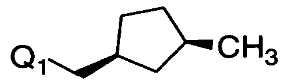
Table 2ae



570

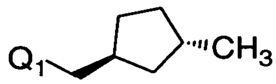


571



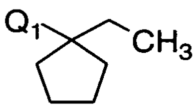
572

573

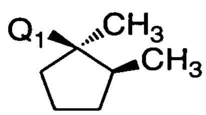


574

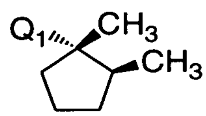
575



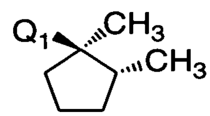
576



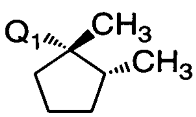
577



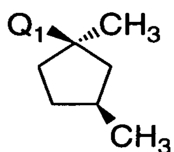
578



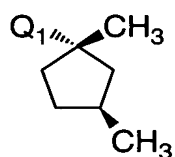
579



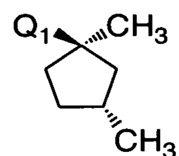
580



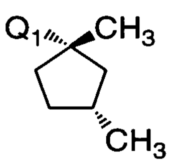
581



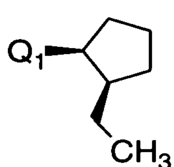
582



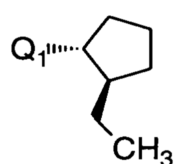
583



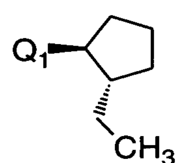
584



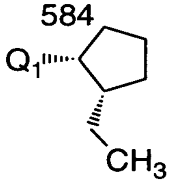
585



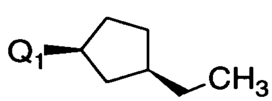
586



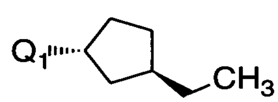
587



588

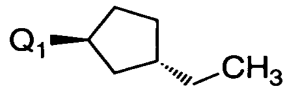


589

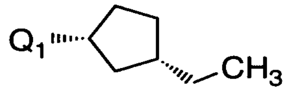


590

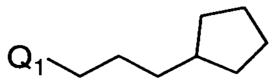
Table 2af



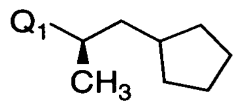
591



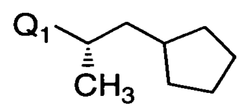
592



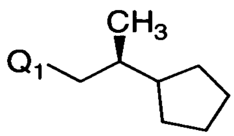
593



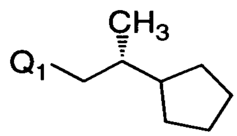
594



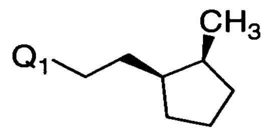
595



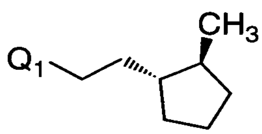
596



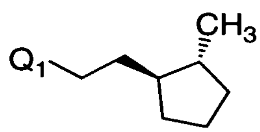
597



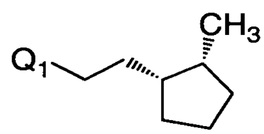
598



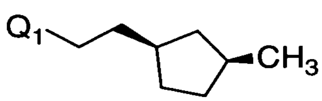
599



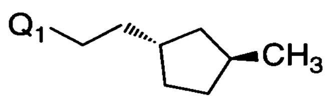
600



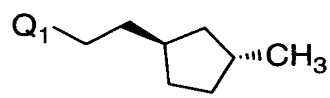
601



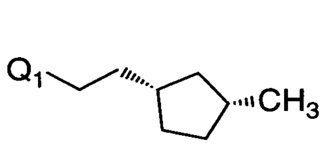
602



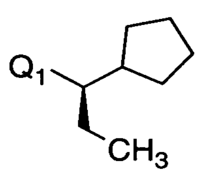
603



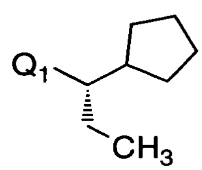
604



605

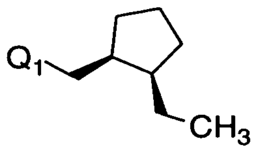


606

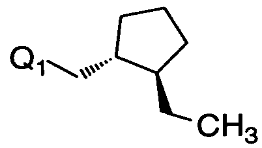


607

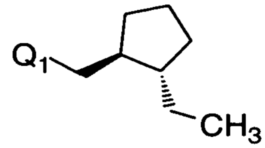
Table 2ag



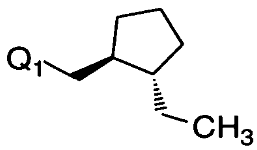
608



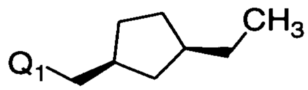
609



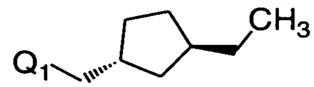
610



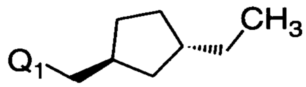
611



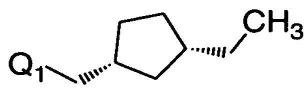
612



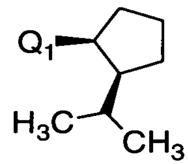
613



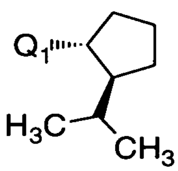
614



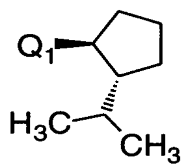
615



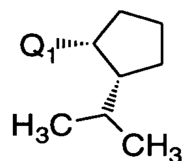
616



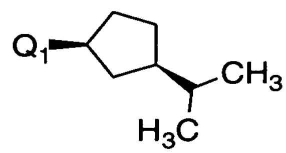
617



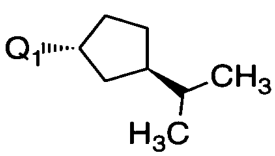
618



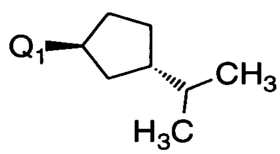
619



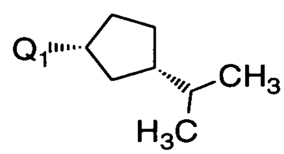
620



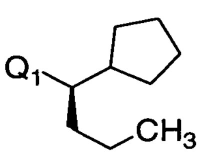
621



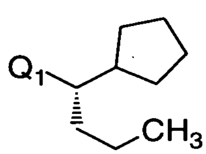
622



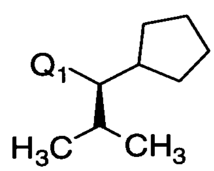
623



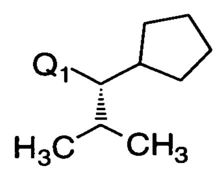
624



625

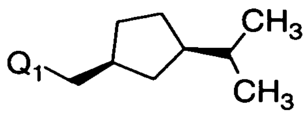


626

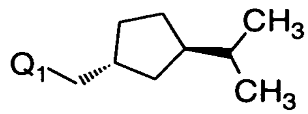


627

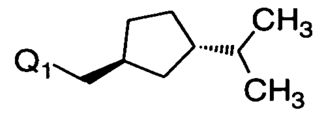
Table 2ah



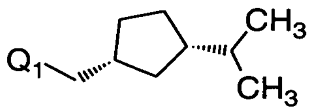
628



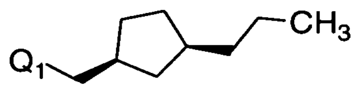
629



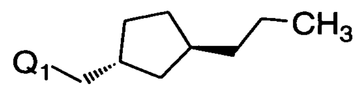
630



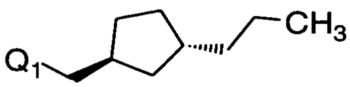
631



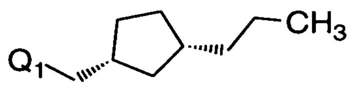
632



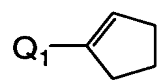
633



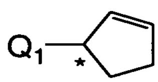
634



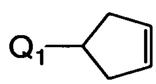
635



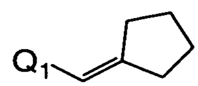
636



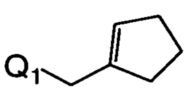
637



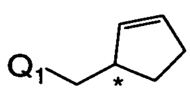
638



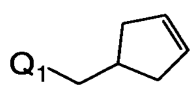
639



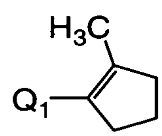
640



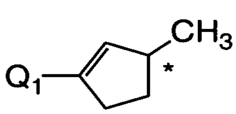
641



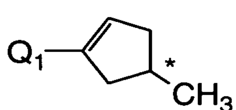
642



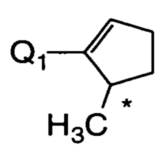
643



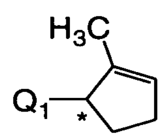
644



645

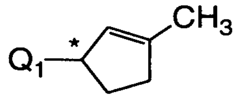


646

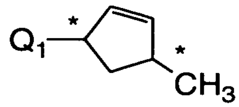


647

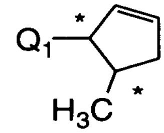
Table 2ai



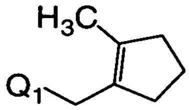
648



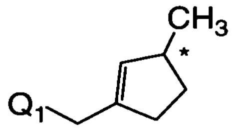
649



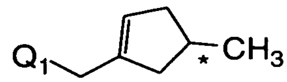
650



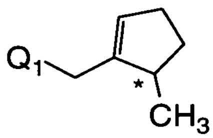
651



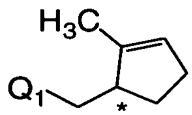
652



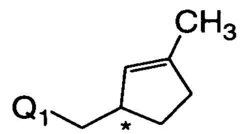
653



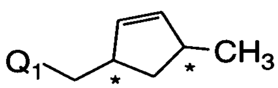
654



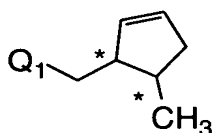
655



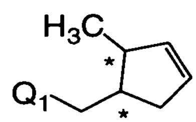
656



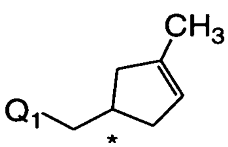
657



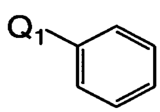
658



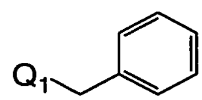
659



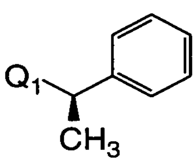
660



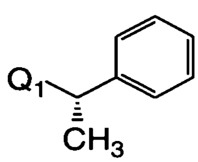
661



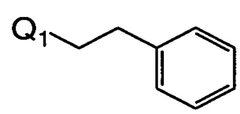
662



663

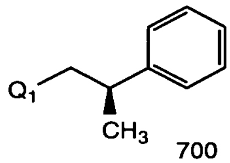


664

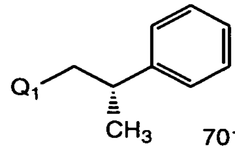


665

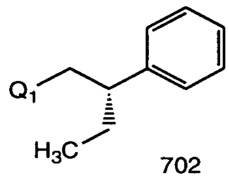
Table 2aj



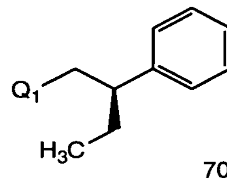
700



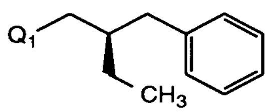
701



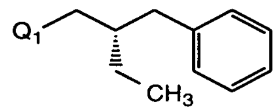
702



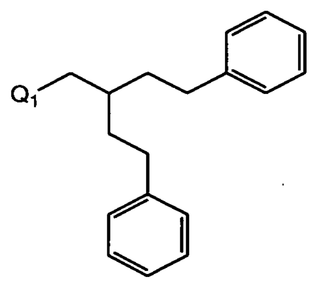
703



704

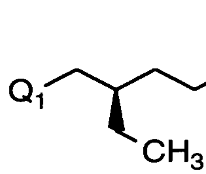


705

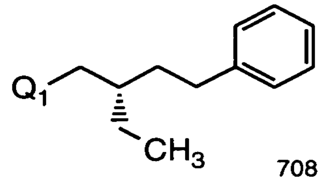


706

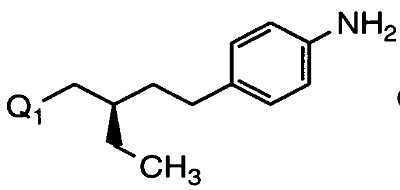
Table 2ak



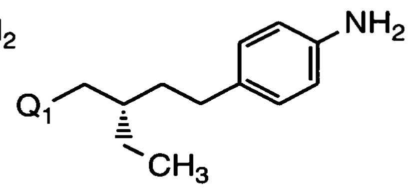
707



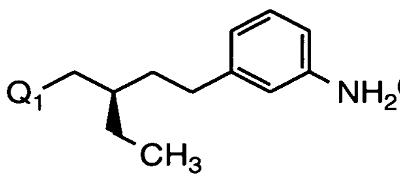
708



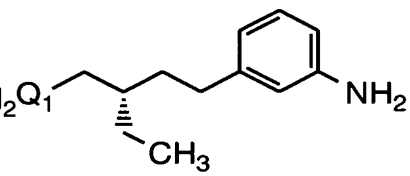
709



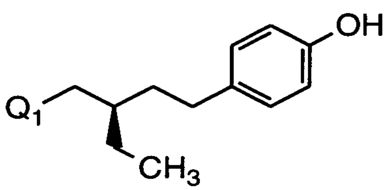
710



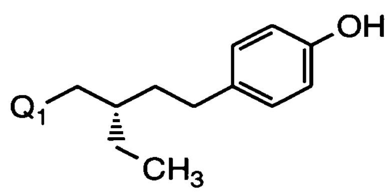
711



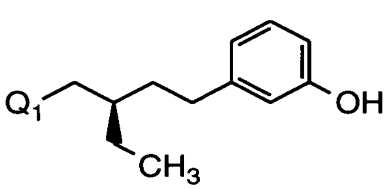
712



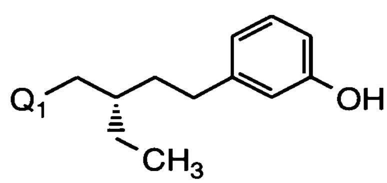
713



714

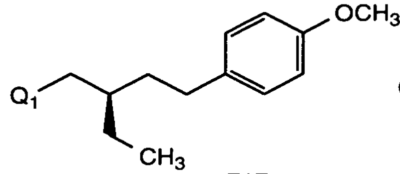


715

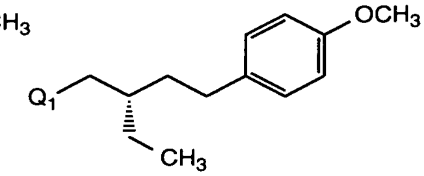


716

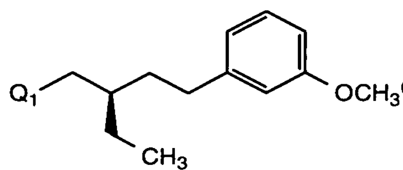
Table 2al



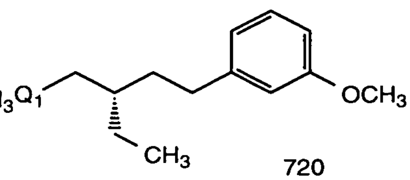
717



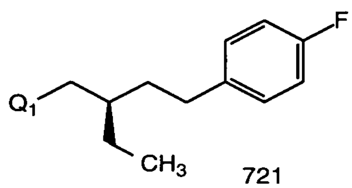
718



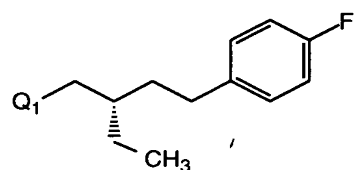
719



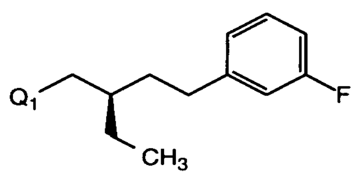
720



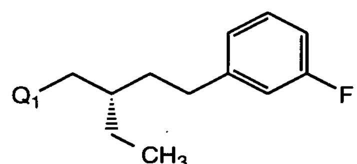
721



722

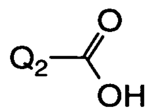


723

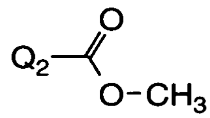


724

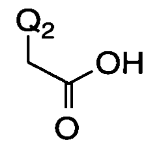
Table 3a



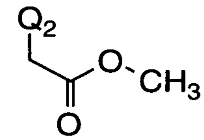
a



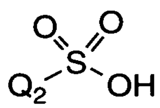
b



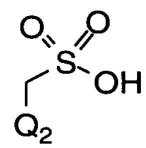
c



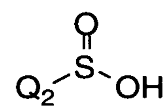
d



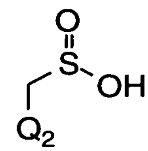
e



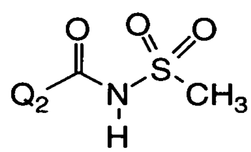
f



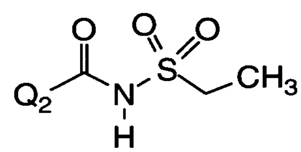
g



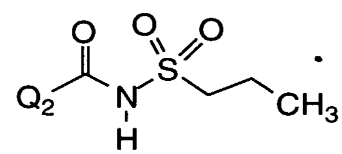
h



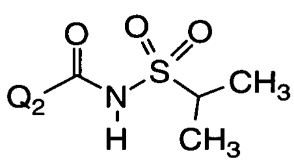
i



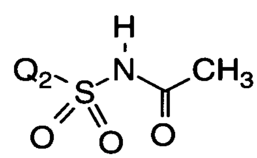
j



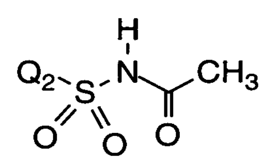
k



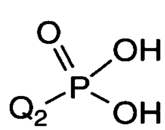
l



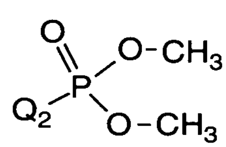
m



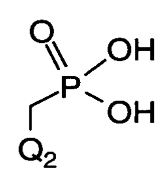
n



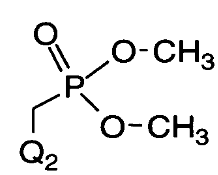
o



p

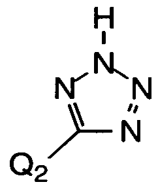


q

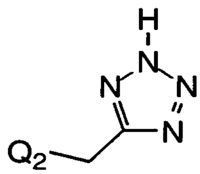


r

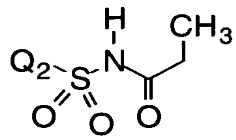
Table 3b



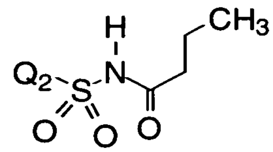
s



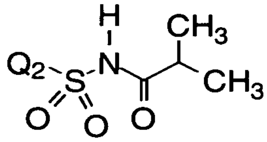
t



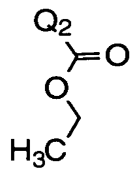
u



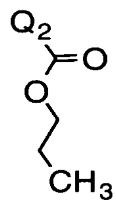
v



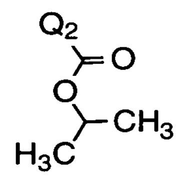
w



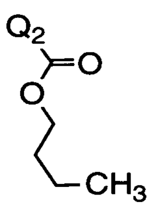
x



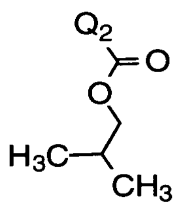
y



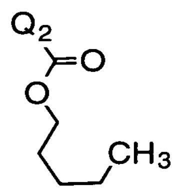
z



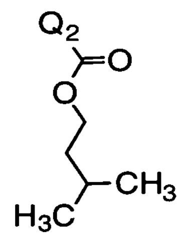
A



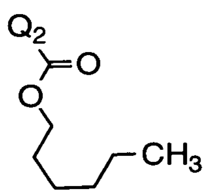
B



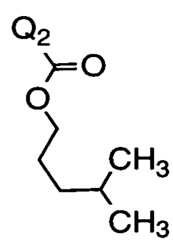
C



D



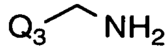
E



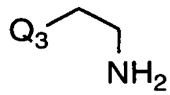
F

Table 4a

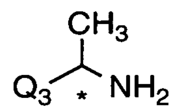
Q_3-OH	Q_3-N_3	Q_3-NO_2	Q_3-NH_2
1	2	3	4



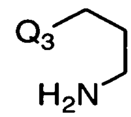
5



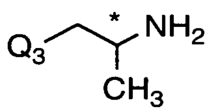
6



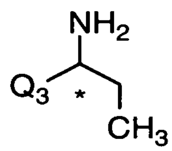
7



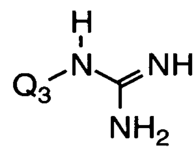
8



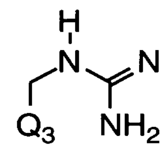
9



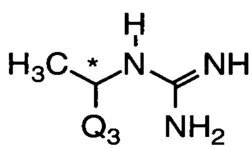
10



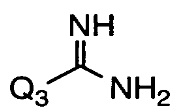
11



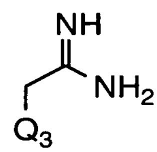
12



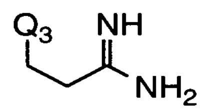
13



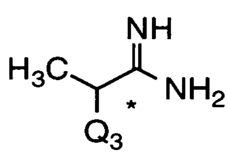
14



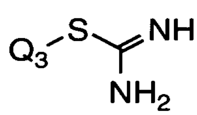
15



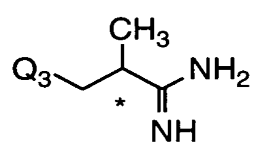
16



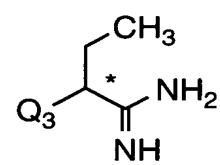
17



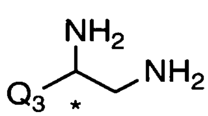
18



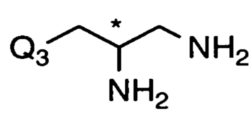
19



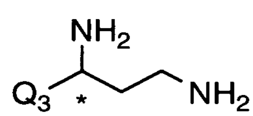
20



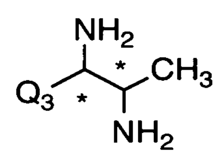
21



22

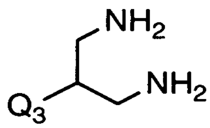


23

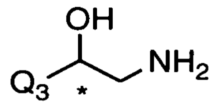


24

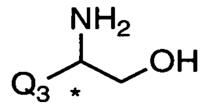
Table 4b



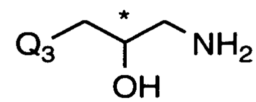
25



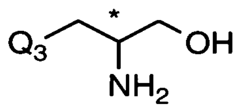
26



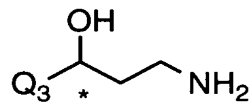
27



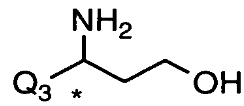
28



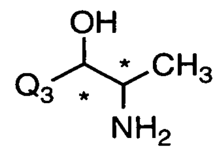
29



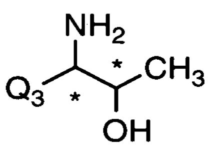
30



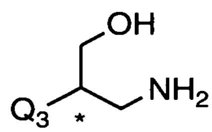
31



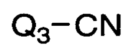
32



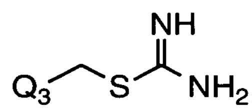
33



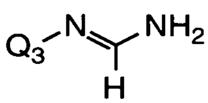
34



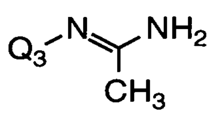
35



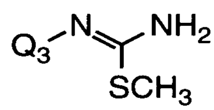
36



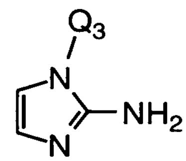
37



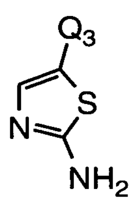
38



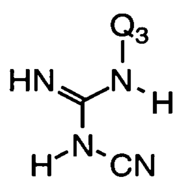
39



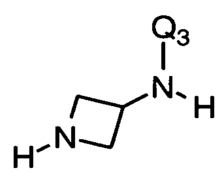
40



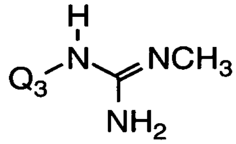
41



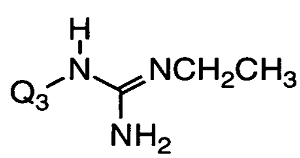
42



43

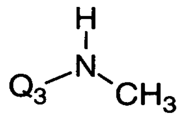


44

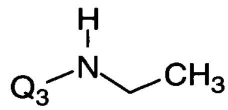


45

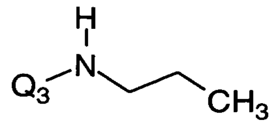
Table 4c



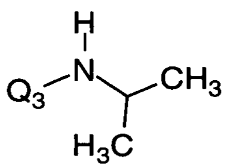
46



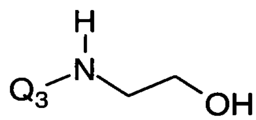
47



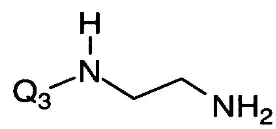
48



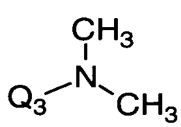
49



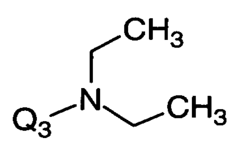
50



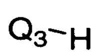
51



52



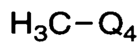
53



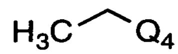
54

Table 5a

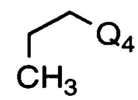
a



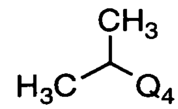
b



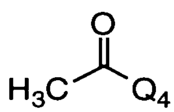
c



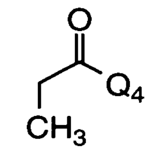
d



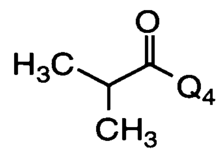
e



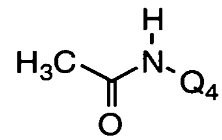
f



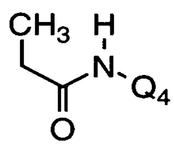
g



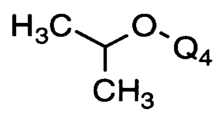
h



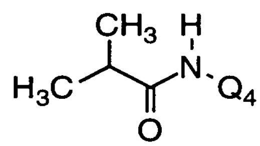
i



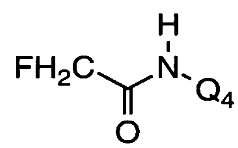
j



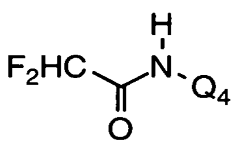
k



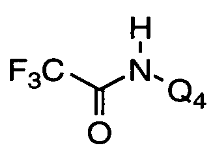
l



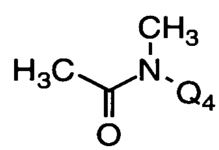
m



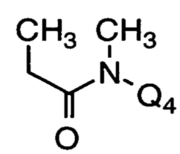
n



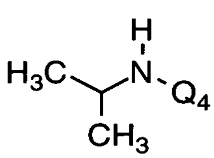
o



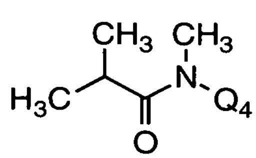
p



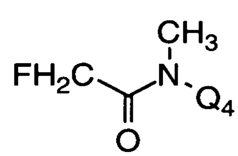
q



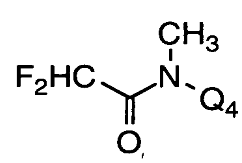
r



s

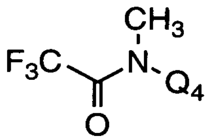


t

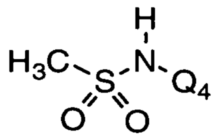


u

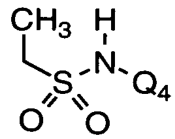
Table 5b



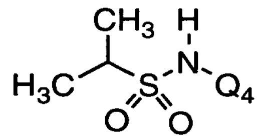
v



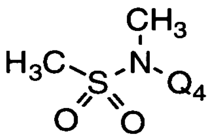
w



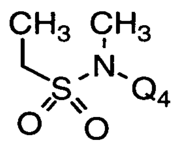
x



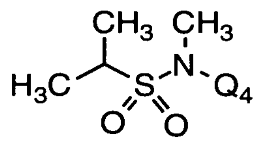
y



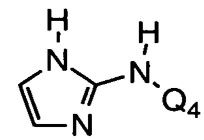
z



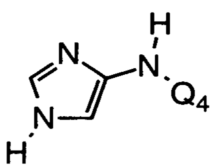
aa



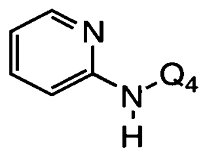
ab



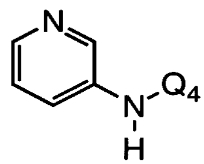
ac



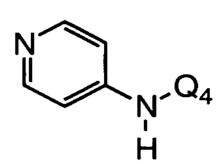
ad



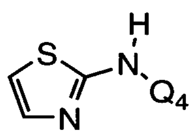
ae



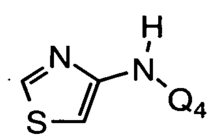
af



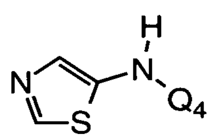
ag



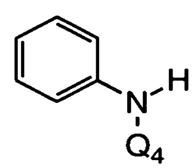
ah



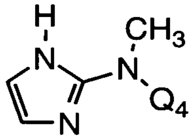
ai



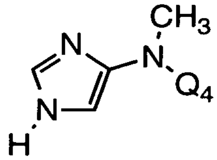
aj



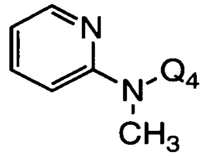
ak



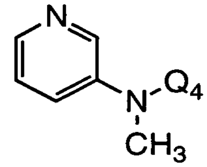
al



am

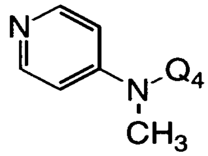


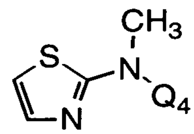
an

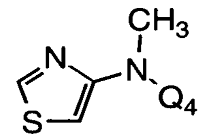


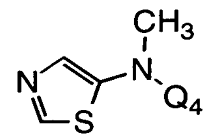
ao

Table 5c

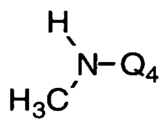

ap

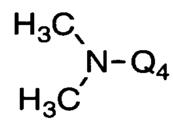

aq

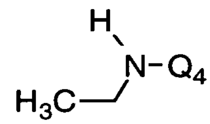

ar

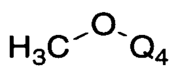

as

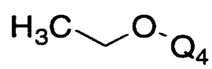
$H_2N{-}Q_4$
at

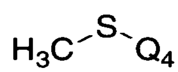

au

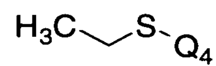

av

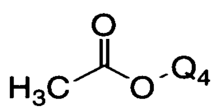

aw

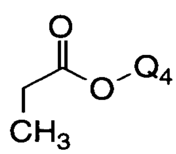

ax

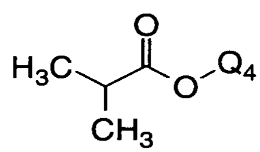

ay

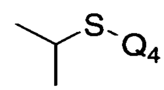

az

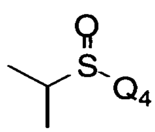

ba

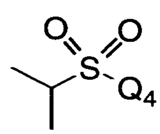

bb

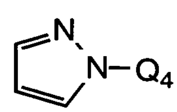

bc

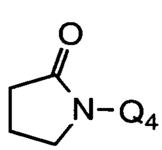

bd

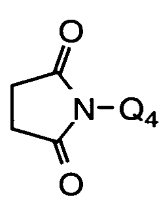

be


bf


bg


bh


bi


bj

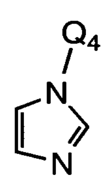

bk

Table 6 - Exemplary Enumerated Compounds

A.3.a.4.i; A.4.a.4.i; A.7.a.4.i; A.9.a.4.i; A.103.a.4.i; A.106.a.4.i; A.107.a.4.i; A.108.a.4.i; A.111.a.4.i; A.114.a.4.i; A.117.a.4.i; A.118.a.4.i; A.119.a.4.i; A.120.a.4.i; A.121.a.4.i; A.137.a.4.i; A.138.a.4.i; A.139.a.4.i; A.140.a.4.i; A.141.a.4.i; A.142.a.4.i; A.145.a.4.i; A.146.a.4.i; A.147.a.4.i; A.148.a.4.i; A.149.a.4.i; A.150.a.4.i; A.151.a.4.i; A.165.a.4.i; A.166.a.4.i; A.167.a.4.i; A.168.a.4.i; A.169.a.4.i; A.170.a.4.i; A.171.a.4.i; A.172.a.4.i; A.173.a.4.i; A.174.a.4.i; A.175.a.4.i; A.176.a.4.i; A.188.a.4.i; A.189.a.4.i; A.190.a.4.i; A.196.a.4.i; A.202.a.4.i; A.205.a.4.i; A.206.a.4.i; A.207.a.4.i; A.208.a.4.i; A.209.a.4.i; A.210.a.4.i; A.211.a.4.i; A.212.a.4.i; A.213.a.4.i; A.700.a.4.i; A.701.a.4.i; A.702.a.4.i; A.703.a.4.i; A.704.a.4.i; A.705.a.4.i; A.706.a.4.i; A.707.a.4.i; A.708.a.4.i; A.709.a.4.i; A.710.a.4.i; A.711.a.4.i; A.712.a.4.i; A.713.a.4.i; A.714.a.4.i; A.715.a.4.i; A.716.a.4.i; A.717.a.4.i; A.718.a.4.i; A.719.a.4.i; A.720.a.4.i; A.721.a.4.i; A.722.a.4.i; A.723.a.4.i; A.724.a.4.i; A.3.a.4.o; A.4.a.4.o; A.7.a.4.o; A.9.a.4.o; A.103.a.4.o; A.106.a.4.o; A.107.a.4.o; A.108.a.4.o; A.111.a.4.o; A.114.a.4.o; A.117.a.4.o; A.118.a.4.o; A.119.a.4.o; A.120.a.4.o; A.121.a.4.o; A.137.a.4.o; A.138.a.4.o; A.139.a.4.o; A.140.a.4.o; A.141.a.4.o; A.142.a.4.o; A.145.a.4.o; A.146.a.4.o; A.147.a.4.o; A.148.a.4.o; A.149.a.4.o; A.150.a.4.o; A.151.a.4.o; A.165.a.4.o; A.166.a.4.o; A.167.a.4.o; A.168.a.4.o; A.169.a.4.o; A.170.a.4.o; A.171.a.4.o; A.172.a.4.o; A.173.a.4.o; A.174.a.4.o; A.175.a.4.o; A.176.a.4.o; A.188.a.4.o; A.189.a.4.o; A.190.a.4.o; A.196.a.4.o; A.202.a.4.o; A.205.a.4.o; A.206.a.4.o; A.207.a.4.o; A.208.a.4.o; A.209.a.4.o; A.210.a.4.o; A.211.a.4.o; A.212.a.4.o; A.213.a.4.o; A.700.a.4.o; A.701.a.4.o; A.702.a.4.o; A.703.a.4.o; A.704.a.4.o; A.705.a.4.o; A.706.a.4.o; A.707.a.4.o; A.708.a.4.o; A.709.a.4.o; A.710.a.4.o; A.711.a.4.o; A.712.a.4.o; A.713.a.4.o; A.714.a.4.o; A.715.a.4.o; A.716.a.4.o; A.717.a.4.o; A.718.a.4.o; A.719.a.4.o; A.720.a.4.o; A.721.a.4.o; A.722.a.4.o; A.723.a.4.o; A.724.a.4.o; A.172.b.4.i; A.173.b.4.i; A.174.b.4.i; A.175.b.4.i; A.176.b.4.i; A.188.b.4.i; A.189.b.4.i; A.190.b.4.i; A.196.b.4.i; A.202.b.4.i; A.205.b.4.i; A.206.b.4.i; A.207.b.4.i; A.208.b.4.i; A.209.b.4.i; A.210.b.4.i; A.211.b.4.i; A.212.b.4.i; A.213.b.4.i; A.700.b.4.i; A.701.b.4.i; A.702.b.4.i; A.703.b.4.i; A.704.b.4.i; A.705.b.4.i; A.706.b.4.i; A.707.b.4.i; A.708.b.4.i; A.709.b.4.i; A.710.b.4.i; A.711.b.4.i; A.712.b.4.i; A.713.b.4.i; A.714.b.4.i; A.715.b.4.i; A.716.b.4.i; A.717.b.4.i; A.718.b.4.i; A.719.b.4.i; A.720.b.4.i; A.721.b.4.i; A.722.b.4.i; A.723.b.4.i; A.724.b.4.i; A.3.b.4.o; A.4.b.4.o; A.7.b.4.o; A.9.b.4.o; A.103.b.4.o; A.106.b.4.o; A.107.b.4.o; A.108.b.4.o; A.111.b.4.o; A.114.b.4.o; A.117.b.4.o; A.118.b.4.o; A.119.b.4.o; A.120.b.4.o; A.121.b.4.o; A.137.b.4.o; A.138.b.4.o; A.139.b.4.o; A.140.b.4.o; A.141.b.4.o; A.142.b.4.o; A.145.b.4.o; A.146.b.4.o; A.147.b.4.o; A.148.b.4.o; A.149.b.4.o; A.150.b.4.o; A.151.b.4.o; A.165.b.4.o; A.166.b.4.o; A.167.b.4.o; A.168.b.4.o; A.169.b.4.o; A.170.b.4.o; A.171.b.4.o; A.172.b.4.o; A.173.b.4.o; A.174.b.4.o; A.175.b.4.o; A.176.b.4.o; A.188.b.4.o; A.189.b.4.o; A.190.b.4.o; A.196.b.4.o; A.202.b.4.o; A.205.b.4.o; A.206.b.4.o; A.207.b.4.o; A.208.b.4.o; A.209.b.4.o; A.210.b.4.o; A.211.b.4.o; A.212.b.4.o; A.213.b.4.o; A.700.b.4.o; A.701.b.4.o; A.702.b.4.o; A.703.b.4.o; A.704.b.4.o; A.705.b.4.o; A.706.b.4.o; A.707.b.4.o; A.708.b.4.o; A.709.b.4.o; A.710.b.4.o; A.711.b.4.o; A.712.b.4.o; A.713.b.4.o; A.714.b.4.o; A.715.b.4.o; A.716.b.4.o; A.717.b.4.o; A.718.b.4.o; A.719.b.4.o; A.720.b.4.o; A.721.b.4.o; A.722.b.4.o; A.723.b.4.o; A.724.b.4.o; A.172.x.4.i; A.173.x.4.i; A.174.x.4.i; A.175.x.4.i; A.176.x.4.i; A.188.x.4.i; A.189.x.4.i; A.190.x.4.i; A.196.x.4.i;

A.202.x.4.i; A.205.x.4.i; A.206.x.4.i; A.207.x.4.i; A.208.x.4.i; A.209.x.4.i; A.210.x.4.i; A.211.x.4.i; A.212.x.4.i; A.213.x.4.i; A.700.x.4.i; A.701.x.4.i; A.702.x.4.i; A.703.x.4.i; A.704.x.4.i; A.705.x.4.i; A.706.x.4.i; A.707.x.4.i; A.708.x.4.i; A.709.x.4.i; A.710.x.4.i; A.711.x.4.i; A.712.x.4.i; A.713.x.4.i; A.714.x.4.i; A.715.x.4.i; A.716.x.4.i; A.717.x.4.i; A.718.x.4.i; A.719.x.4.i; A.720.x.4.i; A.721.x.4.i; A.722.x.4.i; A.723.x.4.i; A.724.x.4.i; A.3.x.4.o; A.4.x.4.o; A.7.x.4.o; A.9.x.4.o; A.103.x.4.o; A.106.x.4.o; A.107.x.4.o; A.108.x.4.o; A.111.x.4.o; A.114.x.4.o; A.117.x.4.o; A.118.x.4.o; A.119.x.4.o; A.120.x.4.o; A.121.x.4.o; A.137.x.4.o; A.138.x.4.o; A.139.x.4.o; A.140.x.4.o; A.141.x.4.o; A.142.x.4.o; A.145.x.4.o; A.146.x.4.o; A.147.x.4.o; A.148.x.4.o; A.149.x.4.o; A.150.x.4.o; A.151.x.4.o; A.165.x.4.o; A.166.x.4.o; A.167.x.4.o; A.168.x.4.o; A.169.x.4.o; A.170.x.4.o; A.171.x.4.o; A.172.x.4.o; A.173.x.4.o; A.174.x.4.o; A.175.x.4.o; A.176.x.4.o; A.188.x.4.o; A.189.x.4.o; A.190.x.4.o; A.196.x.4.o; A.202.x.4.o; A.205.x.4.o; A.206.x.4.o; A.207.x.4.o; A.208.x.4.o; A.209.x.4.o; A.210.x.4.o; A.211.x.4.o; A.212.x.4.o; A.213.x.4.o; A.700.x.4.o; A.701.x.4.o; A.702.x.4.o; A.703.x.4.o; A.704.x.4.o; A.705.x.4.o; A.706.x.4.o; A.707.x.4.o; A.708.x.4.o; A.709.x.4.o; A.710.x.4.o; A.711.x.4.o; A.712.x.4.o; A.713.x.4.o; A.714.x.4.o; A.715.x.4.o; A.716.x.4.o; A.717.x.4.o; A.718.x.4.o; A.719.x.4.o; A.720.x.4.o; A.721.x.4.o; A.722.x.4.o; A.723.x.4.o; A.724.x.4.o; A.172.y.4.i; A.173.y.4.i; A.174.y.4.i; A.175.y.4.i; A.176.y.4.i; A.188.y.4.i; A.189.y.4.i; A.190.y.4.i; A.196.y.4.i; A.202.y.4.i; A.205.y.4.i; A.206.y.4.i; A.207.y.4.i; A.208.y.4.i; A.209.y.4.i; A.210.y.4.i; A.211.y.4.i; A.212.y.4.i; A.213.y.4.i; A.700.y.4.i; A.701.y.4.i; A.702.y.4.i; A.703.y.4.i; A.704.y.4.i; A.705.y.4.i; A.706.y.4.i; A.707.y.4.i; A.708.y.4.i; A.709.y.4.i; A.710.y.4.i; A.711.y.4.i; A.712.y.4.i; A.713.y.4.i; A.714.y.4.i; A.715.y.4.i; A.716.y.4.i; A.717.y.4.i; A.718.y.4.i; A.719.y.4.i; A.720.y.4.i; A.721.y.4.i; A.722.y.4.i; A.723.y.4.i; A.724.y.4.i; A.3.y.4.o; A.4.y.4.o; A.7.y.4.o; A.9.y.4.o; A.103.y.4.o; A.106.y.4.o; A.107.y.4.o; A.108.y.4.o; A.111.y.4.o; A.114.y.4.o; A.117.y.4.o; A.118.y.4.o; A.119.y.4.o; A.120.y.4.o; A.121.y.4.o; A.137.y.4.o; A.138.y.4.o; A.139.y.4.o; A.140.y.4.o; A.141.y.4.o; A.142.y.4.o; A.145.y.4.o; A.146.y.4.o; A.147.y.4.o; A.148.y.4.o; A.149.y.4.o; A.150.y.4.o; A.151.y.4.o; A.165.y.4.o; A.166.y.4.o; A.167.y.4.o; A.168.y.4.o; A.169.y.4.o; A.170.y.4.o; A.171.y.4.o; A.172.y.4.o; A.173.y.4.o; A.174.y.4.o; A.175.y.4.o; A.176.y.4.o; A.188.y.4.o; A.189.y.4.o; A.190.y.4.o; A.196.y.4.o; A.202.y.4.o; A.205.y.4.o; A.206.y.4.o; A.207.y.4.o; A.208.y.4.o; A.209.y.4.o; A.210.y.4.o; A.211.y.4.o; A.212.y.4.o; A.213.y.4.o; A.700.y.4.o; A.701.y.4.o; A.702.y.4.o; A.703.y.4.o; A.704.y.4.o; A.705.y.4.o; A.706.y.4.o; A.707.y.4.o; A.708.y.4.o; A.709.y.4.o; A.710.y.4.o; A.711.y.4.o; A.712.y.4.o; A.713.y.4.o; A.714.y.4.o; A.715.y.4.o; A.716.y.4.o; A.717.y.4.o; A.718.y.4.o; A.719.y.4.o; A.720.y.4.o; A.721.y.4.o; A.722.y.4.o; A.723.y.4.o; A.724.y.4.o; A.172.z.4.i; A.173.z.4.i; A.174.z.4.i; A.175.z.4.i; A.176.z.4.i; A.188.z.4.i; A.189.z.4.i; A.190.z.4.i; A.196.z.4.i; A.202.z.4.i; A.205.z.4.i; A.206.z.4.i; A.207.z.4.i; A.208.z.4.i; A.209.z.4.i; A.210.z.4.i; A.211.z.4.i; A.212.z.4.i; A.213.z.4.i; A.700.z.4.i; A.701.z.4.i; A.702.z.4.i; A.703.z.4.i; A.704.z.4.i; A.705.z.4.i; A.706.z.4.i; A.707.z.4.i; A.708.z.4.i; A.709.z.4.i; A.710.z.4.i; A.711.z.4.i; A.712.z.4.i; A.713.z.4.i; A.714.z.4.i; A.715.z.4.i; A.716.z.4.i; A.717.z.4.i; A.718.z.4.i; A.719.z.4.i; A.720.z.4.i; A.721.z.4.i; A.722.z.4.i; A.723.z.4.i; A.724.z.4.i; A.3.z.4.o; A.4.z.4.o; A.7.z.4.o; A.9.z.4.o; A.103.z.4.o; A.106.z.4.o; A.107.z.4.o; A.108.z.4.o; A.111.z.4.o; A.114.z.4.o; A.117.z.4.o; A.118.z.4.o; A.119.z.4.o; A.120.z.4.o; A.121.z.4.o;

A.137.z.4.o; A.138.z.4.o; A.139.z.4.o; A.140.z.4.o; A.141.z.4.o; A.142.z.4.o; A.145.z.4.o; A.146.z.4.o; A.147.z.4.o; A.148.z.4.o; A.149.z.4.o; A.150.z.4.o; A.151.z.4.o; A.165.z.4.o; A.166.z.4.o; A.167.z.4.o; A.168.z.4.o; A.169.z.4.o; A.170.z.4.o; A.171.z.4.o; A.172.z.4.o; A.173.z.4.o; A.174.z.4.o; A.175.z.4.o; A.176.z.4.o; A.188.z.4.o; A.189.z.4.o; A.190.z.4.o; A.196.z.4.o; A.202.z.4.o; A.205.z.4.o; A.206.z.4.o; A.207.z.4.o; A.208.z.4.o; A.209.z.4.o; A.210.z.4.o; A.211.z.4.o; A.212.z.4.o; A.213.z.4.o; A.700.z.4.o; A.701.z.4.o; A.702.z.4.o; A.703.z.4.o; A.704.z.4.o; A.705.z.4.o; A.706.z.4.o; A.707.z.4.o; A.708.z.4.o; A.709.z.4.o; A.710.z.4.o; A.711.z.4.o; A.712.z.4.o; A.713.z.4.o; A.714.z.4.o; A.715.z.4.o; A.716.z.4.o; A.717.z.4.o; A.718.z.4.o; A.719.z.4.o; A.720.z.4.o; A.721.z.4.o; A.722.z.4.o; A.723.z.4.o; A.724.z.4.o; A.172.A.4.i; A.173.A.4.i; A.174.A.4.i; A.175.A.4.i; A.176.A.4.i; A.188.A.4.i; A.189.A.4.i; A.190.A.4.i; A.196.A.4.i; A.202.A.4.i; A.205.A.4.i; A.206.A.4.i; A.207.A.4.i; A.208.A.4.i; A.209.A.4.i; A.210.A.4.i; A.211.A.4.i; A.212.A.4.i; A.213.A.4.i; A.700.A.4.i; A.701.A.4.i; A.702.A.4.i; A.703.A.4.i; A.704.A.4.i; A.705.A.4.i; A.706.A.4.i; A.707.A.4.i; A.708.A.4.i; A.709.A.4.i; A.710.A.4.i; A.711.A.4.i; A.712.A.4.i; A.713.A.4.i; A.714.A.4.i; A.715.A.4.i; A.716.A.4.i; A.717.A.4.i; A.718.A.4.i; A.719.A.4.i; A.720.A.4.i; A.721.A.4.i; A.722.A.4.i; A.723.A.4.i; A.724.A.4.i; A.3.A.4.o; A.4.A.4.o; A.7.A.4.o; A.9.A.4.o; A.103.A.4.o; A.106.A.4.o; A.107.A.4.o; A.108.A.4.o; A.111.A.4.o; A.114.A.4.o; A.117.A.4.o; A.118.A.4.o; A.119.A.4.o; A.120.A.4.o; A.121.A.4.o; A.137.A.4.o; A.138.A.4.o; A.139.A.4.o; A.140.A.4.o; A.141.A.4.o; A.142.A.4.o; A.145.A.4.o; A.146.A.4.o; A.147.A.4.o; A.148.A.4.o; A.149.A.4.o; A.150.A.4.o; A.151.A.4.o; A.165.A.4.o; A.166.A.4.o; A.167.A.4.o; A.168.A.4.o; A.169.A.4.o; A.170.A.4.o; A.171.A.4.o; A.172.A.4.o; A.173.A.4.o; A.174.A.4.o; A.175.A.4.o; A.176.A.4.o; A.188.A.4.o; A.189.A.4.o; A.190.A.4.o; A.196.A.4.o; A.202.A.4.o; A.205.A.4.o; A.206.A.4.o; A.207.A.4.o; A.208.A.4.o; A.209.A.4.o; A.210.A.4.o; A.211.A.4.o; A.212.A.4.o; A.213.A.4.o; A.700.A.4.o; A.701.A.4.o; A.702.A.4.o; A.703.A.4.o; A.704.A.4.o; A.705.A.4.o; A.706.A.4.o; A.707.A.4.o; A.708.A.4.o; A.709.A.4.o; A.710.A.4.o; A.711.A.4.o; A.712.A.4.o; A.713.A.4.o; A.714.A.4.o; A.715.A.4.o; A.716.A.4.o; A.717.A.4.o; A.718.A.4.o; A.719.A.4.o; A.720.A.4.o; A.721.A.4.o; A.722.A.4.o; A.723.A.4.o; A.724.A.4.o; A.172.B.4.i; A.173.B.4.i; A.174.B.4.i; A.175.B.4.i; A.176.B.4.i; A.188.B.4.i; A.189.B.4.i; A.190.B.4.i; A.196.B.4.i; A.202.B.4.i; A.205.B.4.i; A.206.B.4.i; A.207.B.4.i; A.208.B.4.i; A.209.B.4.i; A.210.B.4.i; A.211.B.4.i; A.212.B.4.i; A.213.B.4.i; A.700.B.4.i; A.701.B.4.i; A.702.B.4.i; A.703.B.4.i; A.704.B.4.i; A.705.B.4.i; A.706.B.4.i; A.707.B.4.i; A.708.B.4.i; A.709.B.4.i; A.710.B.4.i; A.711.B.4.i; A.712.B.4.i; A.713.B.4.i; A.714.B.4.i; A.715.B.4.i; A.716.B.4.i; A.717.B.4.i; A.718.B.4.i; A.719.B.4.i; A.720.B.4.i; A.721.B.4.i; A.722.B.4.i; A.723.B.4.i; A.724.B.4.i; A.3.B.4.o; A.4.B.4.o; A.7.B.4.o; A.9.B.4.o; A.103.B.4.o; A.106.B.4.o; A.107.B.4.o; A.108.B.4.o; A.111.B.4.o; A.114.B.4.o; A.117.B.4.o; A.118.B.4.o; A.119.B.4.o; A.120.B.4.o; A.121.B.4.o; A.137.B.4.o; A.138.B.4.o; A.139.B.4.o; A.140.B.4.o; A.141.B.4.o; A.142.B.4.o; A.145.B.4.o; A.146.B.4.o; A.147.B.4.o; A.148.B.4.o; A.149.B.4.o; A.150.B.4.o; A.151.B.4.o; A.165.B.4.o; A.166.B.4.o; A.167.B.4.o; A.168.B.4.o; A.169.B.4.o; A.170.B.4.o; A.171.B.4.o; A.172.B.4.o; A.173.B.4.o; A.174.B.4.o; A.175.B.4.o; A.176.B.4.o; A.188.B.4.o; A.189.B.4.o; A.190.B.4.o; A.196.B.4.o; A.202.B.4.o; A.205.B.4.o; A.206.B.4.o;

A.207.B.4.o; A.208.B.4.o; A.209.B.4.o; A.210.B.4.o; A.211.B.4.o; A.212.B.4.o; A.213.B.4.o; A.700.B.4.o; A.701.B.4.o; A.702.B.4.o; A.703.B.4.o; A.704.B.4.o; A.705.B.4.o; A.706.B.4.o; A.707.B.4.o; A.708.B.4.o; A.709.B.4.o; A.710.B.4.o; A.711.B.4.o; A.712.B.4.o; A.713.B.4.o; A.714.B.4.o; A.715.B.4.o; A.716.B.4.o; A.717.B.4.o; A.718.B.4.o; A.719.B.4.o; A.720.B.4.o; A.721.B.4.o; A.722.B.4.o; A.723.B.4.o; A.724.B.4.o; B.3.a.54.i; B.4.a.54.i; B.7.a.54.i; B.9.a.54.i; B.103.a.54.i; B.106.a.54.i; B.107.a.54.i; B.108.a.54.i; B.111.a.54.i; B.114.a.54.i; B.117.a.54.i; B.118.a.54.i; B.119.a.54.i; B.120.a.54.i; B.121.a.54.i; B.137.a.54.i; B.138.a.54.i; B.139.a.54.i; B.140.a.54.i; B.141.a.54.i; B.142.a.54.i; B.145.a.54.i; B.146.a.54.i; B.147.a.54.i; B.148.a.54.i; B.149.a.54.i; B.150.a.54.i; B.151.a.54.i; B.165.a.54.i; B.166.a.54.i; B.167.a.54.i; B.168.a.54.i; B.169.a.54.i; B.170.a.54.i; B.171.a.54.i; B.172.a.54.i; B.173.a.54.i; B.174.a.54.i; B.175.a.54.i; B.176.a.54.i; B.188.a.54.i; B.189.a.54.i; B.190.a.54.i; B.196.a.54.i; B.202.a.54.i; B.205.a.54.i; B.206.a.54.i; B.207.a.54.i; B.208.a.54.i; B.209.a.54.i; B.210.a.54.i; B.211.a.54.i; B.212.a.54.i; B.213.a.54.i; B.700.a.54.i; B.701.a.54.i; B.702.a.54.i; B.703.a.54.i; B.704.a.54.i; B.705.a.54.i; B.706.a.54.i; B.707.a.54.i; B.708.a.54.i; B.709.a.54.i; B.710.a.54.i; B.711.a.54.i; B.712.a.54.i; B.713.a.54.i; B.714.a.54.i; B.715.a.54.i; B.716.a.54.i; B.717.a.54.i; B.718.a.54.i; B.719.a.54.i; B.720.a.54.i; B.721.a.54.i; B.722.a.54.i; B.723.a.54.i; B.724.a.54.i; B.3.a.54.o; B.4.a.54.o; B.7.a.54.o; B.9.a.54.o; B.103.a.54.o; B.106.a.54.o; B.107.a.54.o; B.108.a.54.o; B.111.a.54.o; B.114.a.54.o; B.117.a.54.o; B.118.a.54.o; B.119.a.54.o; B.120.a.54.o; B.121.a.54.o; B.137.a.54.o; B.138.a.54.o; B.139.a.54.o; B.140.a.54.o; B.141.a.54.o; B.142.a.54.o; B.145.a.54.o; B.146.a.54.o; B.147.a.54.o; B.148.a.54.o; B.149.a.54.o; B.150.a.54.o; B.151.a.54.o; B.165.a.54.o; B.166.a.54.o; B.167.a.54.o; B.168.a.54.o; B.169.a.54.o; B.170.a.54.o; B.171.a.54.o; B.172.a.54.o; B.173.a.54.o; B.174.a.54.o; B.175.a.54.o; B.176.a.54.o; B.188.a.54.o; B.189.a.54.o; B.190.a.54.o; B.196.a.54.o; B.202.a.54.o; B.205.a.54.o; B.206.a.54.o; B.207.a.54.o; B.208.a.54.o; B.209.a.54.o; B.210.a.54.o; B.211.a.54.o; B.212.a.54.o; B.213.a.54.o; B.700.a.54.o; B.701.a.54.o; B.702.a.54.o; B.703.a.54.o; B.704.a.54.o; B.705.a.54.o; B.706.a.54.o; B.707.a.54.o; B.708.a.54.o; B.709.a.54.o; B.710.a.54.o; B.711.a.54.o; B.712.a.54.o; B.713.a.54.o; B.714.a.54.o; B.715.a.54.o; B.716.a.54.o; B.717.a.54.o; B.718.a.54.o; B.719.a.54.o; B.720.a.54.o; B.721.a.54.o; B.722.a.54.o; B.723.a.54.o; B.724.a.54.o; B.172.b.54.i; B.173.b.54.i; B.174.b.54.i; B.175.b.54.i; B.176.b.54.i; B.188.b.54.i; B.189.b.54.i; B.190.b.54.i; B.196.b.54.i; B.202.b.54.i; B.205.b.54.i; B.206.b.54.i; B.207.b.54.i; B.208.b.54.i; B.209.b.54.i; B.210.b.54.i; B.211.b.54.i; B.212.b.54.i; B.213.b.54.i; B.700.b.54.i; B.701.b.54.i; B.702.b.54.i; B.703.b.54.i; B.704.b.54.i; B.705.b.54.i; B.706.b.54.i; B.707.b.54.i; B.708.b.54.i; B.709.b.54.i; B.710.b.54.i; B.711.b.54.i; B.712.b.54.i; B.713.b.54.i; B.714.b.54.i; B.715.b.54.i; B.716.b.54.i; B.717.b.54.i; B.718.b.54.i; B.719.b.54.i; B.720.b.54.i; B.721.b.54.i; B.722.b.54.i; B.723.b.54.i; B.724.b.54.i; B.3.b.54.o; B.4.b.54.o; B.7.b.54.o; B.9.b.54.o; B.103.b.54.o; B.106.b.54.o; B.107.b.54.o; B.108.b.54.o; B.111.b.54.o; B.114.b.54.o; B.117.b.54.o; B.118.b.54.o; B.119.b.54.o; B.120.b.54.o; B.121.b.54.o; B.137.b.54.o; B.138.b.54.o; B.139.b.54.o; B.140.b.54.o; B.141.b.54.o; B.142.b.54.o; B.145.b.54.o; B.146.b.54.o; B.147.b.54.o; B.148.b.54.o; B.149.b.54.o; B.150.b.54.o; B.151.b.54.o; B.165.b.54.o; B.166.b.54.o; B.167.b.54.o; B.168.b.54.o; B.169.b.54.o; B.170.b.54.o; B.171.b.54.o; B.172.b.54.o; B.173.b.54.o; B.174.b.54.o; B.175.b.54.o; B.176.b.54.o; B.188.b.54.o; B.189.b.54.o; B.190.b.54.o; B.196.b.54.o; B.202.b.54.o;

B.205.b.54.o; B.206.b.54.o; B.207.b.54.o; B.208.b.54.o; B.209.b.54.o; B.210.b.54.o; B.211.b.54.o; B.212.b.54.o; B.213.b.54.o; B.700.b.54.o; B.701.b.54.o; B.702.b.54.o; B.703.b.54.o; B.704.b.54.o; B.705.b.54.o; B.706.b.54.o; B.707.b.54.o; B.708.b.54.o; B.709.b.54.o; B.710.b.54.o; B.711.b.54.o; B.712.b.54.o; B.713.b.54.o; B.714.b.54.o; B.715.b.54.o; B.716.b.54.o; B.717.b.54.o; B.718.b.54.o; B.719.b.54.o; B.720.b.54.o; B.721.b.54.o; B.722.b.54.o; B.723.b.54.o; B.724.b.54.o; B.172.x.54.i; B.173.x.54.i; B.174.x.54.i; B.175.x.54.i; B.176.x.54.i; B.188.x.54.i; B.189.x.54.i; B.190.x.54.i; B.196.x.54.i; B.202.x.54.i; B.205.x.54.i; B.206.x.54.i; B.207.x.54.i; B.208.x.54.i; B.209.x.54.i; B.210.x.54.i; B.211.x.54.i; B.212.x.54.i; B.213.x.54.i; B.700.x.54.i; B.701.x.54.i; B.702.x.54.i; B.703.x.54.i; B.704.x.54.i; B.705.x.54.i; B.706.x.54.i; B.707.x.54.i; B.708.x.54.i; B.709.x.54.i; B.710.x.54.i; B.711.x.54.i; B.712.x.54.i; B.713.x.54.i; B.714.x.54.i; B.715.x.54.i; B.716.x.54.i; B.717.x.54.i; B.718.x.54.i; B.719.x.54.i; B.720.x.54.i; B.721.x.54.i; B.722.x.54.i; B.723.x.54.i; B.724.x.54.i; B.3.x.54.o; B.4.x.54.o; B.7.x.54.o; B.9.x.54.o; B.103.x.54.o; B.106.x.54.o; B.107.x.54.o; B.108.x.54.o; B.111.x.54.o; B.114.x.54.o; B.117.x.54.o; B.118.x.54.o; B.119.x.54.o; B.120.x.54.o; B.121.x.54.o; B.137.x.54.o; B.138.x.54.o; B.139.x.54.o; B.140.x.54.o; B.141.x.54.o; B.142.x.54.o; B.145.x.54.o; B.146.x.54.o; B.147.x.54.o; B.148.x.54.o; B.149.x.54.o; B.150.x.54.o; B.151.x.54.o; B.165.x.54.o; B.166.x.54.o; B.167.x.54.o; B.168.x.54.o; B.169.x.54.o; B.170.x.54.o; B.171.x.54.o; B.172.x.54.o; B.173.x.54.o; B.174.x.54.o; B.175.x.54.o; B.176.x.54.o; B.188.x.54.o; B.189.x.54.o; B.190.x.54.o; B.196.x.54.o; B.202.x.54.o; B.205.x.54.o; B.206.x.54.o; B.207.x.54.o; B.208.x.54.o; B.209.x.54.o; B.210.x.54.o; B.211.x.54.o; B.212.x.54.o; B.213.x.54.o; B.700.x.54.o; B.701.x.54.o; B.702.x.54.o; B.703.x.54.o; B.704.x.54.o; B.705.x.54.o; B.706.x.54.o; B.707.x.54.o; B.708.x.54.o; B.709.x.54.o; B.710.x.54.o; B.711.x.54.o; B.712.x.54.o; B.713.x.54.o; B.714.x.54.o; B.715.x.54.o; B.716.x.54.o; B.717.x.54.o; B.718.x.54.o; B.719.x.54.o; B.720.x.54.o; B.721.x.54.o; B.722.x.54.o; B.723.x.54.o; B.724.x.54.o; B.172.y.54.i; B.173.y.54.i; B.174.y.54.i; B.175.y.54.i; B.176.y.54.i; B.188.y.54.i; B.189.y.54.i; B.190.y.54.i; B.196.y.54.i; B.202.y.54.i; B.205.y.54.i; B.206.y.54.i; B.207.y.54.i; B.208.y.54.i; B.209.y.54.i; B.210.y.54.i; B.211.y.54.i; B.212.y.54.i; B.213.y.54.i; B.700.y.54.i; B.701.y.54.i; B.702.y.54.i; B.703.y.54.i; B.704.y.54.i; B.705.y.54.i; B.706.y.54.i; B.707.y.54.i; B.708.y.54.i; B.709.y.54.i; B.710.y.54.i; B.711.y.54.i; B.712.y.54.i; B.713.y.54.i; B.714.y.54.i; B.715.y.54.i; B.716.y.54.i; B.717.y.54.i; B.718.y.54.i; B.719.y.54.i; B.720.y.54.i; B.721.y.54.i; B.722.y.54.i; B.723.y.54.i; B.724.y.54.i; B.3.y.54.o; B.4.y.54.o; B.7.y.54.o; B.9.y.54.o; B.103.y.54.o; B.106.y.54.o; B.107.y.54.o; B.108.y.54.o; B.111.y.54.o; B.114.y.54.o; B.117.y.54.o; B.118.y.54.o; B.119.y.54.o; B.120.y.54.o; B.121.y.54.o; B.137.y.54.o; B.138.y.54.o; B.139.y.54.o; B.140.y.54.o; B.141.y.54.o; B.142.y.54.o; B.145.y.54.o; B.146.y.54.o; B.147.y.54.o; B.148.y.54.o; B.149.y.54.o; B.150.y.54.o; B.151.y.54.o; B.165.y.54.o; B.166.y.54.o; B.167.y.54.o; B.168.y.54.o; B.169.y.54.o; B.170.y.54.o; B.171.y.54.o; B.172.y.54.o; B.173.y.54.o; B.174.y.54.o; B.175.y.54.o; B.176.y.54.o; B.188.y.54.o; B.189.y.54.o; B.190.y.54.o; B.196.y.54.o; B.202.y.54.o; B.205.y.54.o; B.206.y.54.o; B.207.y.54.o; B.208.y.54.o; B.209.y.54.o; B.210.y.54.o; B.211.y.54.o; B.212.y.54.o; B.213.y.54.o; B.700.y.54.o; B.701.y.54.o; B.702.y.54.o; B.703.y.54.o; B.704.y.54.o; B.705.y.54.o; B.706.y.54.o; B.707.y.54.o; B.708.y.54.o; B.709.y.54.o; B.710.y.54.o; B.711.y.54.o; B.712.y.54.o; B.713.y.54.o; B.714.y.54.o; B.715.y.54.o; B.716.y.54.o; B.717.y.54.o; B.718.y.54.o; B.719.y.54.o; B.720.y.54.o; B.721.y.54.o; B.722.y.54.o;

B.723.y.54.o; B.724.y.54.o; B.172.z.54.i; B.173.z.54.i; B.174.z.54.i; B.175.z.54.i; B.176.z.54.i; B.188.z.54.i; B.189.z.54.i; B.190.z.54.i; B.196.z.54.i; B.202.z.54.i; B.205.z.54.i; B.206.z.54.i; B.207.z.54.i; B.208.z.54.i; B.209.z.54.i; B.210.z.54.i; B.211.z.54.i; B.212.z.54.i; B.213.z.54.i; B.700.z.54.i; B.701.z.54.i; B.702.z.54.i; B.703.z.54.i; B.704.z.54.i; B.705.z.54.i; B.706.z.54.i; B.707.z.54.i; B.708.z.54.i; B.709.z.54.i; B.710.z.54.i; B.711.z.54.i; B.712.z.54.i; B.713.z.54.i; B.714.z.54.i; B.715.z.54.i; B.716.z.54.i; B.717.z.54.i; B.718.z.54.i; B.719.z.54.i; B.720.z.54.i; B.721.z.54.i; B.722.z.54.i; B.723.z.54.i; B.724.z.54.i; B.3.z.54.o; B.4.z.54.o; B.7.z.54.o; B.9.z.54.o; B.103.z.54.o; B.106.z.54.o; B.107.z.54.o; B.108.z.54.o; B.111.z.54.o; B.114.z.54.o; B.117.z.54.o; B.118.z.54.o; B.119.z.54.o; B.120.z.54.o; B.121.z.54.o; B.137.z.54.o; B.138.z.54.o; B.139.z.54.o; B.140.z.54.o; B.141.z.54.o; B.142.z.54.o; B.145.z.54.o; B.146.z.54.o; B.147.z.54.o; B.148.z.54.o; B.149.z.54.o; B.150.z.54.o; B.151.z.54.o; B.165.z.54.o; B.166.z.54.o; B.167.z.54.o; B.168.z.54.o; B.169.z.54.o; B.170.z.54.o; B.171.z.54.o; B.172.z.54.o; B.173.z.54.o; B.174.z.54.o; B.175.z.54.o; B.176.z.54.o; B.188.z.54.o; B.189.z.54.o; B.190.z.54.o; B.196.z.54.o; B.202.z.54.o; B.205.z.54.o; B.206.z.54.o; B.207.z.54.o; B.208.z.54.o; B.209.z.54.o; B.210.z.54.o; B.211.z.54.o; B.212.z.54.o; B.213.z.54.o; B.700.z.54.o; B.701.z.54.o; B.702.z.54.o; B.703.z.54.o; B.704.z.54.o; B.705.z.54.o; B.706.z.54.o; B.707.z.54.o; B.708.z.54.o; B.709.z.54.o; B.710.z.54.o; B.711.z.54.o; B.712.z.54.o; B.713.z.54.o; B.714.z.54.o; B.715.z.54.o; B.716.z.54.o; B.717.z.54.o; B.718.z.54.o; B.719.z.54.o; B.720.z.54.o; B.721.z.54.o; B.722.z.54.o; B.723.z.54.o; B.724.z.54.o; B.172.A.54.i; B.173.A.54.i; B.174.A.54.i; B.175.A.54.i; B.176.A.54.i; B.188.A.54.i; B.189.A.54.i; B.190.A.54.i; B.196.A.54.i; B.202.A.54.i; B.205.A.54.i; B.206.A.54.i; B.207.A.54.i; B.208.A.54.i; B.209.A.54.i; B.210.A.54.i; B.211.A.54.i; B.212.A.54.i; B.213.A.54.i; B.700.A.54.i; B.701.A.54.i; B.702.A.54.i; B.703.A.54.i; B.704.A.54.i; B.705.A.54.i; B.706.A.54.i; B.707.A.54.i; B.708.A.54.i; B.709.A.54.i; B.710.A.54.i; B.711.A.54.i; B.712.A.54.i; B.713.A.54.i; B.714.A.54.i; B.715.A.54.i; B.716.A.54.i; B.717.A.54.i; B.718.A.54.i; B.719.A.54.i; B.720.A.54.i; B.721.A.54.i; B.722.A.54.i; B.723.A.54.i; B.724.A.54.i; B.3.A.54.o; B.4.A.54.o; B.7.A.54.o; B.9.A.54.o; B.103.A.54.o; B.106.A.54.o; B.107.A.54.o; B.108.A.54.o; B.111.A.54.o; B.114.A.54.o; B.117.A.54.o; B.118.A.54.o; B.119.A.54.o; B.120.A.54.o; B.121.A.54.o; B.137.A.54.o; B.138.A.54.o; B.139.A.54.o; B.140.A.54.o; B.141.A.54.o; B.142.A.54.o; B.145.A.54.o; B.146.A.54.o; B.147.A.54.o; B.148.A.54.o; B.149.A.54.o; B.150.A.54.o; B.151.A.54.o; B.165.A.54.o; B.166.A.54.o; B.167.A.54.o; B.168.A.54.o; B.169.A.54.o; B.170.A.54.o; B.171.A.54.o; B.172.A.54.o; B.173.A.54.o; B.174.A.54.o; B.175.A.54.o; B.176.A.54.o; B.188.A.54.o; B.189.A.54.o; B.190.A.54.o; B.196.A.54.o; B.202.A.54.o; B.205.A.54.o; B.206.A.54.o; B.207.A.54.o; B.208.A.54.o; B.209.A.54.o; B.210.A.54.o; B.211.A.54.o; B.212.A.54.o; B.213.A.54.o; B.700.A.54.o; B.701.A.54.o; B.702.A.54.o; B.703.A.54.o; B.704.A.54.o; B.705.A.54.o; B.706.A.54.o; B.707.A.54.o; B.708.A.54.o; B.709.A.54.o; B.710.A.54.o; B.711.A.54.o; B.712.A.54.o; B.713.A.54.o; B.714.A.54.o; B.715.A.54.o; B.716.A.54.o; B.717.A.54.o; B.718.A.54.o; B.719.A.54.o; B.720.A.54.o; B.721.A.54.o; B.722.A.54.o; B.723.A.54.o; B.724.A.54.o; B.172.B.54.i; B.173.B.54.i; B.174.B.54.i; B.175.B.54.i; B.176.B.54.i; B.188.B.54.i; B.189.B.54.i; B.190.B.54.i; B.196.B.54.i; B.202.B.54.i; B.205.B.54.i; B.206.B.54.i; B.207.B.54.i; B.208.B.54.i; B.209.B.54.i;

B.210.B.54.i; B.211.B.54.i; B.212.B.54.i; B.213.B.54.i; B.700.B.54.i; B.701.B.54.i; B.702.B.54.i; B.703.B.54.i; B.704.B.54.i; B.705.B.54.i; B.706.B.54.i; B.707.B.54.i; B.708.B.54.i; B.709.B.54.i; B.710.B.54.i; B.711.B.54.i; B.712.B.54.i; B.713.B.54.i; B.714.B.54.i; B.715.B.54.i; B.716.B.54.i; B.717.B.54.i; B.718.B.54.i; B.719.B.54.i; B.720.B.54.i; B.721.B.54.i; B.722.B.54.i; B.723.B.54.i; B.724.B.54.i; B.3.B.54.o; B.4.B.54.o; B.7.B.54.o; B.9.B.54.o; B.103.B.54.o; B.106.B.54.o; B.107.B.54.o; B.108.B.54.o; B.111.B.54.o; B.114.B.54.o; B.117.B.54.o; B.118.B.54.o; B.119.B.54.o; B.120.B.54.o; B.121.B.54.o; B.137.B.54.o; B.138.B.54.o; B.139.B.54.o; B.140.B.54.o; B.141.B.54.o; B.142.B.54.o; B.145.B.54.o; B.146.B.54.o; B.147.B.54.o; B.148.B.54.o; B.149.B.54.o; B.150.B.54.o; B.151.B.54.o; B.165.B.54.o; B.166.B.54.o; B.167.B.54.o; B.168.B.54.o; B.169.B.54.o; B.170.B.54.o; B.171.B.54.o; B.172.B.54.o; B.173.B.54.o; B.174.B.54.o; B.175.B.54.o; B.176.B.54.o; B.188.B.54.o; B.189.B.54.o; B.190.B.54.o; B.196.B.54.o; B.202.B.54.o; B.205.B.54.o; B.206.B.54.o; B.207.B.54.o; B.208.B.54.o; B.209.B.54.o; B.210.B.54.o; B.211.B.54.o; B.212.B.54.o; B.213.B.54.o; B.700.B.54.o; B.701.B.54.o; B.702.B.54.o; B.703.B.54.o; B.704.B.54.o; B.705.B.54.o; B.706.B.54.o; B.707.B.54.o; B.708.B.54.o; B.709.B.54.o; B.710.B.54.o; B.711.B.54.o; B.712.B.54.o; B.713.B.54.o; B.714.B.54.o; B.715.B.54.o; B.716.B.54.o; B.717.B.54.o; B.718.B.54.o; B.719.B.54.o; B.720.B.54.o; B.721.B.54.o; B.722.B.54.o; B.723.B.54.o; B.724.B.54.o.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{++} and Mg^{++}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically the W_1 group carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4, or organic sulfonic acids, to basic centers, typically amines of group G_1, or to acidic groups such as E_1. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichimetric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the

parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of Neuraminidase.

Another aspect of the invention relates to methods of inhibiting the activity of neuraminidase comprising the step of treating a sample suspected of containing neuraminidase with a compound of the invention.

Compositions of the invention act as inhibitors of neuraminidase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of neuraminidase having a geometry unique to neuraminidase. Compositions binding neuraminidase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. In a typical embodiment the compositions bind neuraminidase with a binding coefficient of less than 10^{-4}M, more typically less than 10^{-6}M, still more typically 10^{-8}M. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of neuraminidase. Accordingly, the invention relates to methods of detecting neuraminidase in a sample suspected of containing neuraminidase comprising the steps of: treating a sample suspected of containing neuraminidase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing neuraminidase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant

cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces neuraminidase, frequently a pathogenic organism such as a virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of neuraminidase after application of the composition can be observed by any method including direct and indirect methods of detecting neuraminidase activity. Quantitative, qualitative, and semiquantitative methods of determining neuraminidase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain neuraminidase include bacteria (Vibrio cholerae, Clostridium perfringens, Streptococcus pneumoniae, and Arthrobacter sialophilus) and viruses (especially orthomyxoviruses or paramyxoviruses such as influenza virus A and B, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus, and sendai virus). Inhibition of neuraminidase activity obtained from or found within any of these organisms is within the objects of this invention. The virology of influenza viruses is described in "Fundamental Virology" (Raven Press, New York, 1986), Chapter 24. The compounds of this invention are useful in the treatment or prophylaxis of such infections in animals, e.g. duck, rodents, or swine, or in man.

However, in screening compounds capable of inhibiting influenza viruses it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays, as shown Table 1 of Chandler et al., supra. Thus, a plaque reduction assay should be the primary screening tool.

Screens for Neuraminidase Inhibitors.

Some of the compounds of the invention will be selective for particular organisms such as bacterial verses viral neuraminidases or

neuraminidase from influenza verses parainfluenza. These compositions are identified by routine screening.

Compositions of the invention are screened for inhibitory activity against neuraminidase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of neuraminidase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5 X 10^{-6} M, typically less than about 1 X 10^{-7} M and preferably less than about 5 X 10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, Itzstein, M. von et al.; "Nature", 363(6428):418-423 (1993), in particular page 420, column 2, full paragraph 3, to page 421, column 2, first partial paragraph, describes a suitable *in vitro* assay of Potier, M.; et al.; "Analyt. Biochem.", 94:287-296 (1979), as modified by Chong, A.K.J.; et al.; "Biochem. Biophys. Acta", 1077:65-71 (1991); and Colman, P. M.; et al.; International Publication No. WO 92/06691 (Int. App. No. PCT/AU90/00501, publication date April 30, 1992) page 34, line 13, to page 35, line 16, describes another useful *in vitro* screen.

In vivo screens have also been described in detail, see Itzstein, M. von et al.; *op. cit.*, in particular page 421, column 2, first full paragraph, to page 423, column 2, first partial paragraph, and Colman, P. M.; et al.; *op. cit.* page 36, lines 1-38, describe suitable *in vivo* screens.

In screening assays used herein, compositions having IC_{50} values greater than 1μM (micromolar) are considered as being inactive against influenza neuraminidase.

Pharmaceutical Formulations and Routes of Administration.

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin,

hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally; it is not necessary to administer them by intrapulmonary or intranasal routes.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active

ingredient may also be presented as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom. In one embodiment acid hydrolysis of the medicament is obviated by use of an enteric coating.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or

without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily

solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of influenza A or B infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active influenza infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, for inhalation the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections of the respiratory system, in particular influenza infection, the compositions of the invention are combined with antivirals (such as amantidine, rimantadine and ribavirin), mucolytics, expectorants, bronchialdilators, antibiotics, antipyretics, or analgesics. Ordinarily, antibiotics, antipyretics, and analgesics are administered together with the compounds of this invention.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a

compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C^{14} or H^{3}) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no neuraminidase inhibitory activity of their own.

Additional Uses for the Compounds of This Invention.

The compounds of this invention, or the biologically active substances produced from these compounds by hydrolysis or metabolism *in vivo*, are used as immunogens or for conjugation to proteins, whereby they serve as components of immunogenic compositions to prepare antibodies capable of binding specifically to the protein, to the compounds or to their metabolic products which retain immunologically recognized epitopes (sites of antibody binding). The immunogenic compositions therefore are useful as intermediates in the preparation of antibodies for use in diagnostic, quality control, or the like, methods or in assays for the compounds or their novel metabolic products. The compounds are useful for raising antibodies against otherwise non-immunogenic polypeptides, in that the compounds serve as haptenic sites stimulating an immune response that cross-reacts with the unmodified conjugated protein.

The hydrolysis products of interest include products of the hydrolysis of the protected acidic and basic groups discussed above. As noted above, the acidic or basic amides comprising immunogenic polypeptides such as albumin or keyhole limpet hemocyanin generally are useful as immunogens. The metabolic products described above may retain a substantial degree of

immunological cross reactivity with the compounds of the invention. Thus, the antibodies of this invention will be capable of binding to the unprotected compounds of the invention without binding to the protected compounds; alternatively the metabolic products, will be capable of binding to the protected compounds and/or the metabolitic products without binding to the protected compounds of the invention, or will be capable of binding specifically to any one or all three. The antibodies desirably will not substantially cross-react with naturally-occurring materials. Substantial cross-reactivity is reactivity under specific assay conditions for specific analytes sufficient to interfere with the assay results.

The immunogens of this invention contain the compound of this invention presenting the desired epitope in association with an immunogenic substance. Within the context of the invention such association means covalent bonding to form an immunogenic conjugate (when applicable) or a mixture of non-covalently bonded materials, or a combination of the above. Immunogenic substances include adjuvants such as Freund's adjuvant, immunogenic proteins such as viral, bacterial, yeast, plant and animal polypeptides, in particular keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin or soybean trypsin inhibitor, and immunogenic polysaccharides. Typically, the compound having the structure of the desired epitope is covalently conjugated to an immunogenic polypeptide or polysaccharide by the use of a polyfunctional (ordinarily bifunctional) cross-linking agent. Methods for the manufacture of hapten immunogens are conventional per se, and any of the methods used heretofore for conjugating haptens to immunogenic polypeptides or the like are suitably employed here as well, taking into account the functional groups on the precursors or hydrolytic products which are available for cross-linking and the likelihood of producing antibodies specific to the epitope in question as opposed to the immunogenic substance.

Typically the polypeptide is conjugated to a site on the compound of the invention distant from the epitope to be recognized.

The conjugates are prepared in conventional fashion. For example, the cross-linking agents N-hydroxysuccinimide, succinic anhydride or alkN=C=Nalk are useful in preparing the conjugates of this invention. The conjugates comprise a compound of the invention attached by a bond or a linking group of 1-100, typically, 1-25, more typically 1-10 carbon atoms to the

immunogenic substance. The conjugates are separated from starting materials and by products using chromatography or the like, and then are sterile filtered and vialed for storage.

The compounds of this invention are cross-linked for example through any one or more of the following groups: a hydroxyl group of W_6; a carboxyl group of E_1; a carbon atom of W_6, E_1, G_1, or T_1, in substitution of H; and an amine group of G_1. Included within such compounds are amides of polypeptides where the polypeptide serves as an above-described R_{6c} or R_{6b} groups.

Animals are typically immunized against the immunogenic conjugates or derivatives and antisera or monoclonal antibodies prepared in conventional fashion.

The compounds of the invention are useful for maintaining the structural integrity of glycoproteins in recombinant cell culture, i.e., they are added to fermentations in which glycoproteins are being produced for recovery so as to inhibit neuraminidase-catalyzed cleavage of the desired glycoproteins. This is of particular value in the recombinant synthesis of proteins in heterologous host cells that may disadvantageously degrade the carbohydrate portion of the protein being synthesized.

The compounds of the invention are polyfunctional. As such they represent a unique class of monomers for the synthesis of polymers. By way of example and not limitation, the polymers prepared from the compounds of this invention include polyamides and polyesters.

The present compounds are used as monomers to provide access to polymers having unique pendent functionalities. The compounds of this invention are useful in homopolymers, or as comonomers with monomers which do not fall within the scope of the invention. Homopolymers of the compounds of this invention will have utility as cation exchange agents (polyesters or polyamides) in the preparation of molecular sieves (polyamides), textiles, fibers, films, formed articles and the like where the acid functionality E_1 is esterified to a hydroxyl group in W_6, for example, whereby the pendant basic group G_1 is capable of binding acidic functionalities such as are found in polypeptides whose purification is desired. Polyamides are prepared by cross-linking E_1 and G_1, with W_6 and the adjacent portion of the ring remaining free to function as a hydrophilic or hydrophobic affinity group, depending up the selection of the W_6 group. The preparation of these

polymers from the compounds of the invention is conventional per se.

The compounds of the invention are also useful as a unique class of polyfunctional surfactants. Particularly when W_6 does not contain a hydrophilic substituent and is, for example, alkyl or alkoxy, the compounds have the properties of bi-functional surfactants. As such they have useful surfactant, surface coating, emulsion modifying, rheology modifying and surface wetting properties.

As polyfunctional compounds with defined geometry and carrying simultaneously polar and non-polar moieties, the compounds of the invention are useful as a unique class of phase transfer agents. By way of example and not limitation, the compounds of the invention are useful in phase transfer catalysis and liquid/liquid ion extraction (LIX).

The compounds of the invention optionally contain asymmetric carbon atoms in groups W_6, E_1, G_1, and T_1. As such, they are a unique class of chiral auxiliaries for use in the synthesis or resolution of other optically active materials. For example, a racemic mixture of carboxylic acids can be resolved into its component enantiomers by: 1) forming a mixture of diastereomeric esters or amides with a compound of the invention wherein W_6 is an asymmetric hydroxyalkane or amino alkane group; 2) separating the diastereomers; and 3) hydrolyzing the ester structure. Racemic alcohols are separated by ester formation with an acid group of E_1. Further, such a method can be used to resolve the compounds of the invention themselves if optically active acids or alcohols are used instead of racemic starting materials.

The compounds of this invention are useful as linkers or spacers in preparing affinity absorption matrices, immobilized enzymes for process control, or immunoassay reagents. The compounds herein contain a multiplicity of functional groups that are suitable as sites for cross-linking desired substances. For example, it is conventional to link affinity reagents such as hormones, peptides, antibodies, drugs, and the like to insoluble substrates. These insolublized reagents are employed in known fashion to absorb binding partners for the affinity reagents from manufactured preparations, diagnostic samples and other impure mixtures. Similarly, immobilized enzymes are used to perform catalytic conversions with facile recovery of enzyme. Bifunctional compounds are commonly used to link analytes to detectable groups in preparing diagnostic reagents.

Many functional groups in the compounds of this invention are

suitable for use in cross-linking. For example, the carboxylic or phosphonic acid of group E_1 is used to form esters with alcohols or amides with amines of the reagent to be cross-linked. The G_1 sites substituted with OH, NHR_1, SH, azido (which is reduced to amino if desired before cross-linking), CN, NO_2, amino, guanidino, halo and the like are suitable sites. Suitable protection of reactive groups will be used where necessary while assembling the cross-linked reagent to prevent polymerization of the bifunctional compound of this invention. In general, the compounds here are used by linking them through carboxylic or phosphonic acid to the hydroxyl or amino groups of the first linked partner, then covalently bonded to the other binding partner through a T_1 or G_1 group. For example a first binding partner such as a steroid hormone is esterified to the carboxylic acid of a compound of this invention and then this conjugate is cross-linked through a G_1 hydroxyl to cyanogen bromide activated Sepaharose, whereby immobilized steroid is obtained. Other chemistries for conjugation are well known. See for example Maggio, "Enzyme-Immunoassay" (CRC, 1988, pp 71-135) and references cited therein.

As noted above, the therapeutically useful compounds of this invention in which the W_1, or G_1 carboxyl, hydroxyl or amino groups are protected are useful as oral or sustained release forms. In these uses the protecting group is removed *in vivo*, e.g., hydrolyzed or oxidized, so as to yield the free carboxyl, amino or hydroxyl. Suitable esters or amides for this utility are selected based on the substrate specificity of esterases and/or carboxypeptidases expected to be found within cells where precursor hydrolysis is desired. To the extent that the specificity of these enzymes is unknown, one will screen a plurality of the compounds of this invention until the desired substrate specificity is found. This will be apparent from the appearance of free compound or of antiviral activity. One generally selects amides or esters of the invention compound that are (i) not hydrolyzed or hydrolyzed comparatively slowly in the upper gut, (ii) gut and cell permeable and (iii) hydrolyzed in the cell cytoplasm and/or systemic circulation. Screening assays preferably use cells from particular tissues that are susceptible to influenza infection, e.g. the mucous membranes of the bronchopulmonary tract. Assays known in the art are suitable for determining *in vivo* bioavailability including intestinal lumen stability, cell permeation, liver homogenate stability and plasma stability assays. However,

even if the ester, amide or other protected derivatives are not converted *in vivo* to the free carboxyl, amino or hydroxyl groups, they remain useful as chemical intermediates.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, workup procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Workup typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

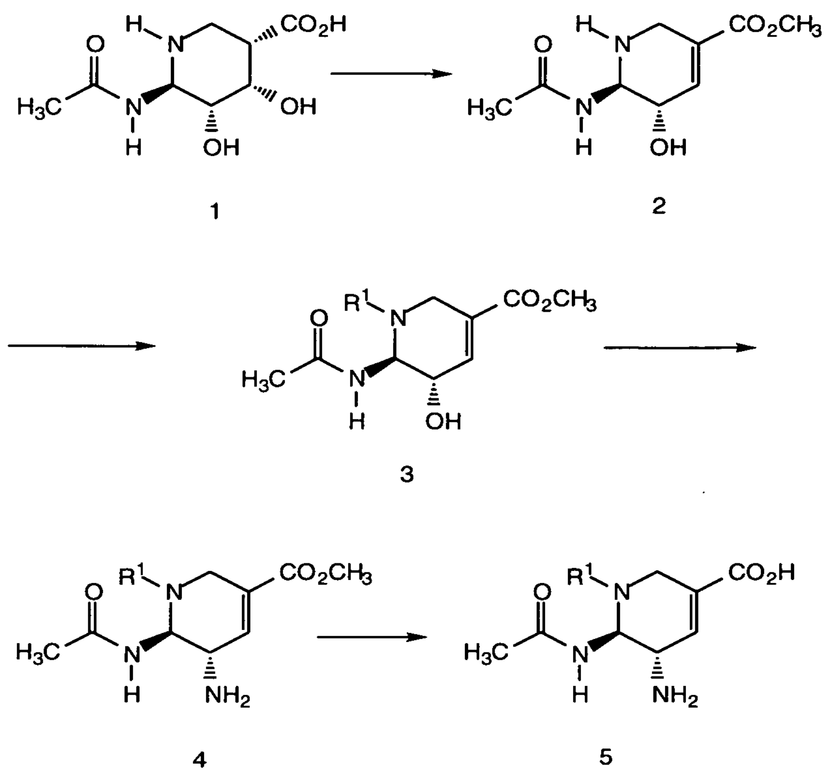
Exemplary methods of preparing the compounds of the invention are shown in the Schemes below.

General aspects of these exemplary methods are described below. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsecquent processes.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive),,etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic sysnthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Scheme 1

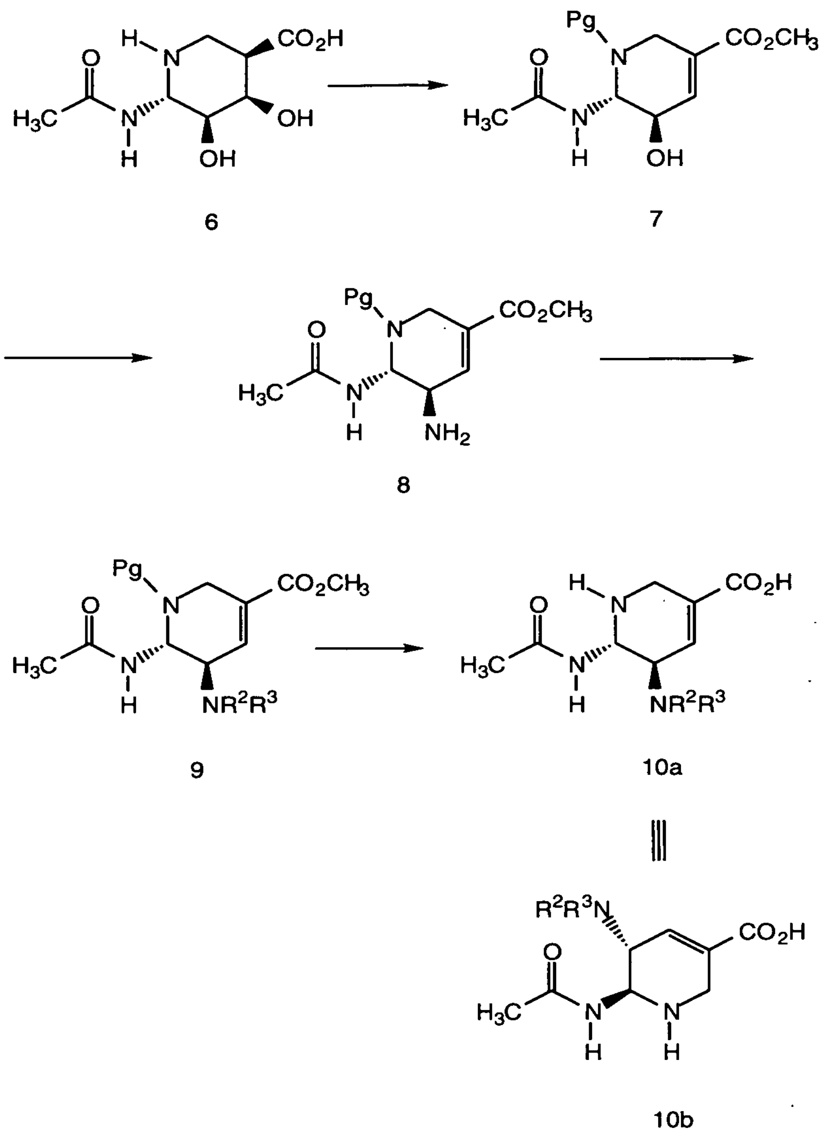


In one embodiment, compounds of the invention are prepared as depicted in **Scheme 1**. Siastatin B (1) from natural materials (Umezawa, H; et al.; J. Antibiotics, **1974**, 27, 963-969) or ribose (Nishimura, Y.; et al.; J. Am. Chem. Soc., **1988**, 110, 7249-7250; and Bull. Chem. Soc. Jpn., **1992**, 65, 978-986) is available in either enantiomer. Conversion to compound 2 is accomplished by known methods (Nishimura, Y.; et al.; J. Antibiotics, **1993**, 46(2), 300-309). Reductive alkylation to form 3 is accomplished by known methods (Nishimura, Y.; et al.; J. Antibiotics, **1992**, 45(10), 1662-1668). Conversion of the alcohol 3 to the amine 4 is accomplished by the methods of Zbiral, E.; et al.; Liebigs Ann. Chem., **1991**, 129-134; and von Itzstein, M.; et al.; Carbohydrate Res., **1993**, 244, 181-185. Deprotection provides compound 5.

By way of example and not limitation, compounds 5 wherein R^1 is ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-ethyl-1-butyl ($-CH_2CH(CH_2CH_3)_2$), 2-ethyl-4-

phenyl-1-butyl (-$CH_2CH(CH_2CH_3)(CH_2CH_2Ph)$), or 2-(2-phenylethyl)-4-phenyl-1-butyl (-$CH_2CH(CH_2CH_2Ph)_2$) are prepared by the method of **Scheme 1**.

Scheme 2

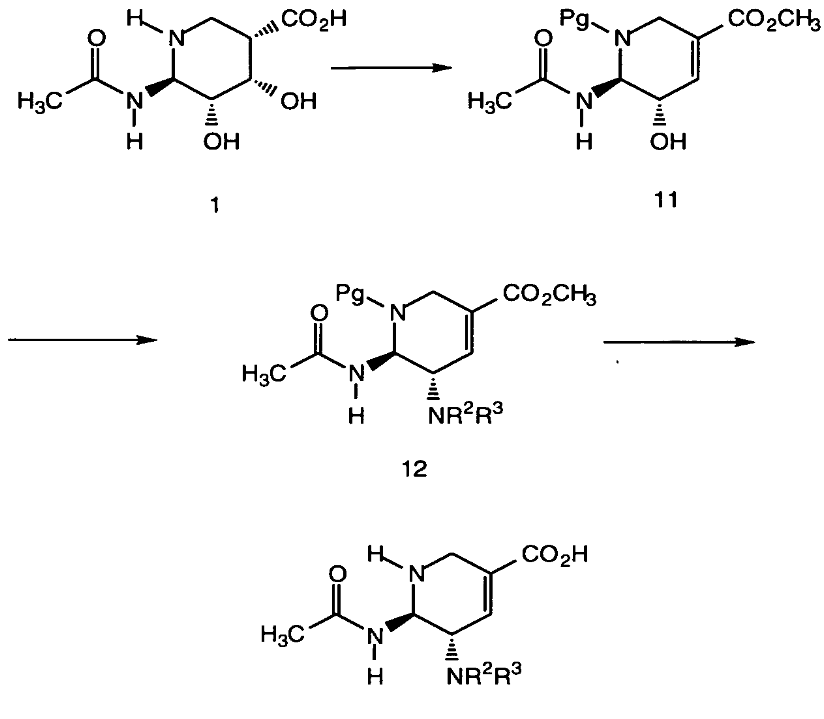


In another embodiment, compounds of the invention are prepared as depicted in **Scheme 2**. The enantiomer of Siastatin B (6) is prepared from from ribose (Nishimura, Y.; et al.; J. Am. Chem. Soc., **1988**, 110, 7249-7250; and Bull. Chem. Soc. Jpn., **1992**, 65, 978-986). Conversion to protected compound 7 is accomplished by known methods (e.g. Pg is Boc, Nishimura, Y.; et al.; J. Antibiotics, **1993**, 46(2), 300-309). Conversion of the alcohol 7 to the amine 8 is accomplished by the methods of Zbiral, E.; et al.; Liebigs Ann. Chem., **1991**, 129-134; and von Itzstein, M.; et al.; Carbohydrate Res., **1993**, 244, 181-185.

Reductive alkylation to form 9 is accomplished by known methods (Nishimura, Y.; et al.; J. Antibiotics, **1992**, 45(10), 1662-1668). Deprotection provides compound 10a. Compound 10a is compound 10b

By way of example and not limitation, compounds 10b wherein R^2 is H and R^3 is ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-ethyl-1-butyl ($-CH_2CH(CH_2CH_3)_2$), 2-ethyl-4-phenyl-1-butyl ($-CH_2CH(CH_2CH_3)(CH_2CH_2Ph)$), or 2-(2-phenylethyl)-4-phenyl-1-butyl ($-CH_2CH(CH_2CH_2Ph)_2$) are prepared by the method of **Scheme 2.**

Scheme 3



1

11

12

13

In another embodiment, compounds of the invention are prepared as depicted in **Scheme 3**. Siastatin B (1) from natural materials (Umezawa, H; et al.; J. Antibiotics, **1974**, 27, 963-969) or ribose (Nishimura, Y.; et al.; J. Am. Chem. Soc., **1988**, 110, 7249-7250; and Bull. Chem. Soc. Jpn., **1992**, 65, 978-986) is available in either enantiomer. Conversion to protected compound 11 is accomplished by known methods (e.g. Pg is Boc, Nishimura, Y.; et al.; J. Antibiotics, **1993**, 46(2), 300-309). Conversion of the alcohol 11 to the amine is accomplished by the methods of Zbiral, E.; et al.; Liebigs Ann. Chem., **1991**, 129-134; and von Itzstein, M.; et al.; Carbohydrate Res., **1993**, 244, 181-185 and reductive alkylation to form 12 is accomplished by known methods (Nishimura, Y.; et al.; J. Antibiotics, **1992**, 45(10), 1662-1668). Deprotection provides compound 13.

By way of example and not limitation, compounds 13 wherein R^2 is H and R^3 is ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl

($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-ethyl-1-butyl ($-CH_2CH(CH_2CH_3)_2$), 2-ethyl-4-phenyl-1-butyl ($-CH_2CH(CH_2CH_3)(CH_2CH_2Ph)$), or 2-(2-phenylethyl)-4-phenyl-1-butyl ($-CH_2CH(CH_2CH_2Ph)_2$) are prepared by the method of **Scheme 3**.

Modification of the exemplary starting materials to form different E_1 groups has been described in detail and will not be elaborated here. See Fleet, G.W.J. et al.; "J. Chem. Soc. Perkin Trans. I", 905-908 (1984), Fleet, G.W.J. et al.; "J. Chem. Soc., Chem. Commun.", 849-850 (1983), Yee, Ying K. et al.; "J. Med. Chem.", 33:2437-2451 (1990); Olson, R.E. et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2229-2234 (1994); Santella, J.B. III et al.; "Bioorganic & Medicinal Chemistry Letters", 4(18):2235-2240 (1994); Judd, D.B. et al.; "J. Med. Chem.", 37:3108-3120 (1994) and Lombaert, S. De et al.; "Bioorganic & Medicinal Chemistry Letters", 5(2):151-154 (1994).

The E_1 sulfur analogs of the carboxylic acid compounds of the invention are prepared by any of the standard techniques. By way of example and not limitation, the carboxylic acids are reduced to the alcohols by standard methods. The alcohols are converted to halides or sulfonic acid esters by standard methods and the resulting compounds are reacted with NaSH to produce the sulfide product. Such reactions are described in Patai, "The Chemistry of the Thiol Group" (John Wiley, New York, 1974), pt. 2, and in particular pages 721-735.

Modifications of each of the above schemes leads to various analogs of the specific exemplary materials produced above. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the above exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such

reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.

All literature and patent citations above are hereby expressly incorporated by reference in their entirety at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.